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(54) Title: METHODS OF TREATING OR PREVENTING SLEEP APNEA (57) Abstract <p>This invention provides methods for the treatment or prevention of sleep apnea in a mammal which comprise administering to a mammal in need thereof an effective amount of a substituted benzimidazole, or a pharmaceutically acceptable salt or solvate thereof.</p>			

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Title**METHODS OF TREATING OR PREVENTING
SLEEP APNEA**

5

Background of the Invention

10 Tachykinins are a family of peptides which share a common amidated carboxy terminal sequence. Substance P was the first peptide of this family to be isolated, although its purification and the determination of its primary sequence did not occur until the early 1970's.

15 Between 1983 and 1984 several groups reported the isolation of two novel mammalian tachykinins, now termed neurokinin A (also known as substance K, neuromedin L, and neurokinin α), and neurokinin B (also known as neuromedin K and neurokinin β). See, J.E. Maggio, Peptides, 6 (Supplement 3):237-243 (1985) for a review of these discoveries.

20 Tachykinins are widely distributed in both the central and peripheral nervous systems, are released from nerves, and exert a variety of biological actions, which, in most cases, depend upon activation of specific receptors expressed on the membrane of target cells. Tachykinins are also produced by a number of non-neural tissues.

25 The mammalian tachykinins substance P, neurokinin A, and neurokinin B act through three major receptor subtypes, denoted as NK-1, NK-2, and NK-3, respectively. These receptors are present in a variety of organs.

30 Substance P is believed inter alia to be involved in the neurotransmission of pain sensations, including the pain associated with migraine headaches and with arthritis. These peptides have also been implicated in gastrointestinal disorders and diseases of the gastrointestinal tract such as inflammatory bowel disease. Tachykinins have also been implicated as playing a role in numerous other maladies, as discussed infra.

35 Tachykinins play a major role in mediating the sensation and transmission of pain or nociception, especially migraine

headaches. see, e.g., S.L. Shepheard, et al., British Journal of Pharmacology, 108:11-20 (1993); S.M. Moussaoui, et al., European Journal of Pharmacology, 238:421-424 (1993); and W.S. Lee, et al., British Journal of Pharmacology, 112:920-924 (1994).

5 In view of the wide number of clinical maladies associated with an excess of tachykinins, the development of tachykinin receptor antagonists will serve to control these clinical conditions. The earliest tachykinin receptor antagonists were peptide derivatives. These antagonists proved to be of limited pharmaceutical utility because of 10 their metabolic instability.

Recent publications have described novel classes of non-peptidyl tachykinin receptor antagonists which generally have greater 15 oral bioavailability and metabolic stability than the earlier classes of tachykinin receptor antagonists. Examples of such newer non-peptidyl tachykinin receptor antagonists are found in United States Patent 5,328,927, issued July 12, 1994; United States Patent 5,360,820, issued November 1, 1994; United States Patent 5,344,830, issued September 6, 1994; United States Patent 5,331,089, issued July 19, 1994; European Patent Publication 591,040 A1, published April 6, 1994; Patent 20 Cooperation Treaty publication WO 94/01402, published January 20, 1994; Patent Cooperation Treaty publication WO 94/04494, published March 3, 1994; and Patent Cooperation Treaty publication WO 93/011609, published January 21, 1993.

Sleep apnea is a condition in which apnea coours during 25 sleep without subjective symptom. It is more prevailing in male middle- and old-aged persons in their forties and fifties. Approximately one per 100 persons is reported to suffer from this condition. In sleep apena there is repeated many times in sleep a sequence of 20-40 seconds apnea, about 10-20 seconds pneusis, and 20-40 seconds apnea. For example, 30 during a 6.5 hour sleep, approximately 400 occurrences of apnea may occur.

As a result of sleep apnea there occur phenomena, such as daytime sleepiness, loss of energy or appetite, swelling in the lower part of the body, and shortness of breath. Increase in leukocyte number, 35 development of polycythemia, and even cardiomegaly are associated with severe instances of sleep apnea. Sleep apnea is observed not only in

- 3 -

adults of middle or advanced age, but also in infants, and may be an indirect cause of hypertension, cardiac insufficiency, and arrhythmia, possibly being a leading cause of sudden infant death syndrome.

Several thousand apparently healthy infants (children 5 under the age of one year) die each year in the United States from Sudden Infant Death Syndrome (SIDS). Deaths from SIDS have been estimated at 7,000 to 10,000 per year. The occurrence of SIDS in a given family can be particularly devastating emotionally because, in general, there is no warning that the infant is at risk and the parent or care giver 10 has no knowledge of any problem until he or she discovers an unconscious or deceased infant thought to be safely sleeping in its crib.

Therapies currently adopted for sleep apnea include bodyweight reduction, pressure application through the nose, surgical operation, and the use of a drug, such as acetazolamide. United States 15 Patent 5,422,374, issued June 6, 1995, describes the use of ubidecarenone to treat sleep apnea. United States Patent 5,356,934, issued October 18, 1994, describes the use of serotonin agonists, most preferably (R)-fluoxetine, to treat sleep apnea. Both of these patents are herein incorporated by reference.

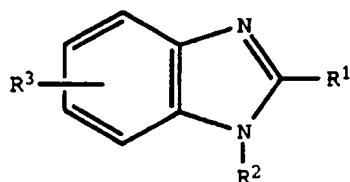
20 Because of the current dissatisfaction of the currently marketed treatments for sleep apnea within the affected population, there exists a need for a more efficacious and safe treatment.

Summary of the Invention

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This invention provides methods for the treatment or prevention of sleep apnea in a mammal which comprise administering to a mammal in need thereof an effective amount of a compound of Formula I

30



I

wherein:

5 R¹ is hydrogen, C₁-C₁₂ alkyl, C₁-C₆ alkoxy, phenyl, C₃-C₈ cycloalkyl, naphthyl, heterocyclic, unsaturated heterocyclic, phenyl-(C₁-C₆ alkylidenyl)-, naphthyl-(C₁-C₆ alkylidenyl)-, heterocyclic-(C₁-C₆ alkylidenyl)-, unsaturated heterocyclic-(C₁-C₆ alkylidenyl)-, phenyl-(C₁-C₆ alkoxy)-, naphthyl-(C₁-C₆ alkoxy)-, heterocyclic-(C₁-C₆ alkoxy)-, or unsaturated heterocyclic-(C₁-C₆ alkoxy)-,

10

15 any one of which phenyl, naphthyl, heterocyclic, C₃-C₈ cycloalkyl, or unsaturated heterocyclic groups may be optionally substituted with one, two, or three moieties independently selected from group consisting of heterocyclic-(C₁-C₆ alkylidenyl)-, unsaturated heterocyclic-(C₁-C₆ alkylidenyl)-, hydroxy, halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, trifluoromethyl, nitro, amino, cyano, C₁-C₆ alkylamino, and C₁-C₆ alkylthio;

20

25 R² is hydrogen, C₁-C₁₂ alkyl, C₁-C₆ alkoxy, phenyl, C₃-C₈ cycloalkyl, naphthyl, heterocyclic, unsaturated heterocyclic, phenyl-(C₁-C₆ alkylidenyl)-, naphthyl-(C₁-C₆ alkylidenyl)-, heterocyclic-(C₁-C₆ alkylidenyl)-, unsaturated heterocyclic-(C₁-C₆ alkylidenyl)-, phenyl-(C₁-C₆ alkoxy)-, naphthyl-(C₁-C₆ alkoxy)-, heterocyclic-(C₁-C₆ alkoxy)-, or unsaturated heterocyclic-(C₁-C₆ alkoxy)-,

30

35 any one of which phenyl, naphthyl, heterocyclic, C₃-C₈ cycloalkyl, or unsaturated heterocyclic groups may be optionally substituted with one, two, or three moieties independently selected from group consisting of phenyl-(C₁-C₆ alkylidenyl)-, naphthyl-(C₁-C₆ alkylidenyl)-, heterocyclic-(C₁-C₆ alkylidenyl)-, unsaturated heterocyclic-(C₁-C₆ alkylidenyl)-, phenyl-

- 5 -

(C₁-C₆ alkoxy)-, naphthyl-(C₁-C₆ alkoxy)-, heterocyclic-(C₁-C₆ alkoxy)-, or unsaturated heterocyclic-(C₁-C₆ alkoxy)-, hydroxy, halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, trifluoromethyl, nitro, amino, cyano, C₁-C₆ alkylamino, and C₁-C₆ alkylthio;

5

R³ is hydrogen, nitro, C₁-C₆ alkanoyl, amino, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₈ cycloalkyl, heterocyclic, unsaturated heterocyclic, halo, C₁-C₆ alkylthio, hydroxy-(C₁-C₆ alkylidенyl)-, hydroxy-(C₁-C₆ alkylidенyl)amino-, R⁴R⁵N-, R⁴R⁵N-(C₁-C₆ alkylidенyl)-, R⁴R⁵N-(C₁-C₆ alkoxy)-, hydroxy-(C₁-C₆ alkyl)-, heterocyclic-(C₁-C₆ alkoxy)-, amino(C₁-C₆ alkylidенyl)-, or trifluoromethyl,

10

where R⁴ and R⁵ are independently selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkanoyl, aryl, heterocyclic, unsaturated heterocyclic, aryl(C₁-C₆ alkylidенyl)-, heterocyclic(C₁-C₆ alkylidенyl)-, unsaturated heterocyclic(C₁-C₆ alkylidенyl)-, and hydrogen or R⁴ and R⁵ combine to form C₃-C₈ cycloalkyl,

15

any one of which alkyl or alkoxy groups may be substituted with one or more halo, amino, or nitro, and

20

any one of which aryl, unsaturated heterocyclic, or heterocyclic groups may be substituted with one, two, or three moieties independently selected from group consisting of hydroxy, halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, trifluoromethyl, nitro, amino, cyano, C₃-C₈ cycloalkyl, C₁-C₆ alkylamino, and C₁-C₆ alkylthio;

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- 6 -

with the proviso that not more than one of R¹ and R² may be hydrogen;

5 or a pharmaceutically acceptable salt or solvate thereof, in combination with another analgesic whose primary mechanism of action is not as a tachykinin receptor antagonist.

Detailed Description and Preferred Embodiments

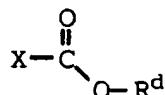
10 The terms and abbreviations used in the instant examples have their normal meanings unless otherwise designated. For example "°C" refers to degrees Celsius; "N" refers to normal or normality; "mol" refers to mole or moles; "mmol" refers to millimole or millimoles; "g" refers to gram or grams; "kg" refers to kilogram or kilograms; "L" refers to liter or liters; "ml" means milliliter or milliliters; "M" refers to molar or molarity; "MS" refers to mass spectrometry; and "NMR" refers to nuclear magnetic resonance spectroscopy.

15

As used herein, the term "C₁-C₆ alkyl" refers to straight or branched, monovalent, saturated aliphatic chains of 1 to 6 carbon atoms and includes, but is not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, and hexyl. The term "C₁-C₆ alkyl" includes within its definition the term "C₁-C₃ alkyl".

20 "Halo" represents chloro, fluoro, bromo or iodo.

25 The term "haloformate" as used herein refers to an ester of a haloformic acid, this compound having the formula



30 wherein X is halo, and R^d is C₁-C₆ alkyl. Preferred haloformates are bromoformates and chloroformates. Especially preferred are chloroformates. Those haloformates wherein R^d is C₃-C₆ alkyl are especially preferred. Most preferred is isobutylchloroformate.

The term "unsaturated heterocycle" represents a stable 5- to 7-membered monocyclic or 7- to 10-membered bicyclic heterocyclic ring which has one or more double bonds and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of 5 nitrogen, oxygen or sulfur, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized and including a bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The unsaturated heterocyclic ring may be attached at any heteroatom or 10 carbon atom which affords a stable structure.

Examples of such heterocycles and unsaturated heterocycles include piperidinyl, piperazinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridyl, pyrazinyl, pyrimidinyl, 15 pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, quinuclidinyl, isothiazolidinyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, thiadiazolyl, benzopyranyl, benzothiazolyl, benzoazolyl, furyl, tetrahydrofuryl, tetrahydropyranyl, thienyl, benzothienyl, 20 thiamorpholinyl, thiamorpholinyl-sulfoxide, thiamorpholinylsulfone, oxadiazolyl, triazolyl, tetrahydroquinolinyl, and tetrahydroisoquinolinyl.

"C₁-C₆ alkoxy" represents a straight or branched alkyl chain having from one to six carbon atoms attached to an oxygen atom. Typical C₁-C₆ alkoxy groups include methoxy, ethoxy, propoxy, 25 isopropoxy, butoxy, *t*-butoxy, pentoxy and the like. The term "C₁-C₆ alkoxy" includes within its definition the term "C₁-C₄ alkoxy".

"C₂-C₆ alkanoyl" represents a straight or branched alkyl chain having from one to five carbon atoms attached to a carbonyl moiety. Typical C₂-C₆ alkanoyl groups include acetyl, propanoyl, 30 isopropanoyl, butanoyl, *t*-butanoyl, pentanoyl, hexanoyl, 3-methylpentanoyl and the like.

"C₃-C₈ cycloalkyl" represents a saturated hydrocarbon ring structure containing from three to eight carbon atoms which is unsubstituted. Typical C₃-C₈ cycloalkyl groups include cyclopropyl, 35 cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl.

The term "hydroxy-protecting groups" as used herein refers to substituents of the hydroxy group commonly employed to block or protect the hydroxy functionality while reacting other functional groups on the compound. Examples of such hydroxy-protecting groups include

5 methoxymethyl, benzyloxymethyl, methoxyethoxymethyl, 2-(trimethylsilyl)ethoxymethyl, methylthiomethyl, 2,2-dichloro-1,1-difluoroethyl, tetrahydropyranyl, phenacyl, cyclopropylmethyl, allyl, C₁-C₆ alkyl, 2,6-dimethylbenzyl, o-nitrobenzyl, 4-picolyl, dimethylsilyl, t-butyldimethylsilyl, levulinate, pivaloate, benzoate, dimethylsulfonate,

10 dimethylphosphinyl, isobutyrate, adamantoate and tetrahydropyranyl. Further examples of these groups may be found in T. W. Greene and P.G.M. Wuts, **PROTECTIVE GROUPS IN ORGANIC SYNTHESIS**, (1991) at Chapter 3.

The compounds prepared in the processes of the present invention have an asymmetric center. As a consequence of this chiral center, the compounds produced in the present invention may occur as racemates, mixtures of enantiomers and as individual enantiomers, as well as diastereomers and mixtures of diastereomers. Processes for preparing such asymmetric forms, individual isomers and combinations thereof, are within the scope of the present invention.

The terms "R" and "S" are used herein as commonly used in organic chemistry to denote specific configuration of a chiral center. The term "R" (*rectus*) refers to that configuration of a chiral center with a clockwise relationship of group priorities (highest to second lowest) when viewed along the bond toward the lowest priority group. The term "S" (*sinister*) refers to that configuration of a chiral center with a counterclockwise relationship of group priorities (highest to second lowest) when viewed along the bond toward the lowest priority group. The priority of groups is based upon their atomic number (in order of decreasing atomic number). A partial list of priorities and a discussion of stereochemistry is contained in **NOMENCLATURE OF ORGANIC COMPOUNDS: PRINCIPLES AND PRACTICE**, (J.H. Fletcher, *et al.*, eds., 1974) at pages 103-120.

In addition to the (R)-(S) system, the older D-L system is also used in this document to denote absolute configuration, especially with reference to amino acids. In this system a Fischer projection formula is

5 oriented so that the number 1 carbon of the main chain is at the top. The prefix "D" is used to represent the absolute configuration of the isomer in which the functional (determining) group is on the right side of the carbon atom at the chiral center and "L", that of the isomer in which it is on the left.

10 As noted supra, this invention includes methods employing the pharmaceutically acceptable salts of the compounds defined by Formula I. A compound of this invention can possess a sufficiently acidic, a sufficiently basic, or both functional groups, and accordingly react with any of a number of organic and inorganic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt.

15 The term "pharmaceutically acceptable salt" as used herein, refers to salts of the compounds of the above formula which are substantially non-toxic to living organisms. Typical pharmaceutically acceptable salts include those salts prepared by reaction of the compounds of the present invention with a pharmaceutically acceptable mineral or organic acid or an organic or inorganic base. Such salts are known as acid addition and base addition salts.

20 Acids commonly employed to form acid addition salts are inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids such as *p*-toluenesulfonic, methanesulfonic acid, oxalic acid, *p*-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid, and the like. Examples of such
25 pharmaceutically acceptable salts are the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, hydrochloride, dihydrochloride, isobutyrate, caproate, heptanoate, propionate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, hydroxybenzoate, methoxybenzoate, phthalate, sulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, γ -hydroxybutyrate, glycolate, tartrate,
30 methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate and the like. Preferred
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- 10 -

pharmaceutically acceptable acid addition salts are those formed with mineral acids such as hydrochloric acid and hydrobromic acid, and those formed with organic acids such as maleic acid and methanesulfonic acid.

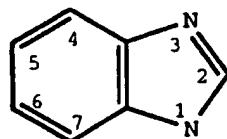
5 Base addition salts include those derived from inorganic bases, such as ammonium or alkali or alkaline earth metal hydroxides, carbonates, bicarbonates, and the like. Such bases useful in preparing the salts of this invention thus include sodium hydroxide, potassium hydroxide, ammonium hydroxide, potassium carbonate, sodium carbonate, sodium bicarbonate, potassium bicarbonate, calcium hydroxide, calcium carbonate, and the like. The potassium and sodium salt forms are particularly preferred.

10

15 It should be recognized that the particular counterion forming a part of any salt of this invention is usually not of a critical nature, so long as the salt as a whole is pharmacologically acceptable and as long as the counterion does not contribute undesired qualities to the salt as a whole.

20 This invention further encompasses methods employing the pharmaceutically acceptable solvates of the compounds of Formula I. Many of the compounds of Formula I can combine with solvents such as water, methanol, ethanol and acetonitrile to form pharmaceutically acceptable solvates such as the corresponding hydrate, methanolate, ethanolate and acetonitrilate.

25 The compounds of the present invention are derivatives of benzimidazole which are named and numbered according to the Ring Index, The American Chemical Society, as follows.



30 The preferred methods of this invention employ those compounds of Formula I wherein:

a) R¹ is phenyl, naphthyl, heterocyclic, unsubstituted heterocyclic, or substituted derivatives thereof;

5 b) R² is phenyl, heterocyclic, unsaturated heterocyclic, phenyl(C₁-C₆ alkylidenyl)-, heterocyclic(C₁-C₆ alkylidenyl)-, unsaturated heterocyclic(C₁-C₆ alkylidenyl)-, or substituted derivatives thereof;

10 c) R³ is R⁴R⁵N-(C₁-C₆ alkylidenyl)-, C₁-C₆ alkanoyl, , C₁-C₄ alkoxy, imidazole, amino-(C₁-C₆ alkylidenyl), hydroxy-(C₁-C₆ alkylidenyl)amino-, heterocyclic-(C₁-C₆ alkoxy)-, R⁴R⁵N-(C₁-C₆ alkoxy)-, or hydroxy;

15 d) R³ is at the 5 or 6 position of the benzimidazole.

16 The especially preferred methods of this invention employ those compounds of Formula I wherein:

20 a) R¹ is phenyl or naphthyl substituted with one or more electron donating, lipophilic substituents;

b) R² is substituted benzyl or substituted phenyl;

25 c) R³ is R⁴R⁵N-(C₁-C₆ alkylidenyl)-, heterocyclic-(C₁-C₆ alkoxy)-, R⁴R⁵N-(C₁-C₆ alkoxy)-, or unsaturated heterocyclic(C₁-C₆ alkylidenyl)-; and

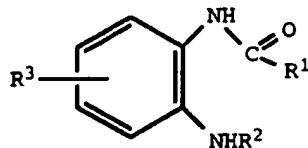
d) R³ is at the 6 position of the benzimidazole.

30 The steps of this synthesis are described in European Patent Application Publication 694,535, to be published January 31, 1996.

35 The compounds of Formula I can be prepared by processes known in the literature. See, e.g., G.W.H. Cheeseman and R.F. Cookson, THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS, (A. Weissberger, et al., eds. 1979). The usual process for the preparation of

- 12 -

the compounds of Formula I is by cyclization of an appropriately substituted o-phenylenediamine such as the one depicted in Formula III



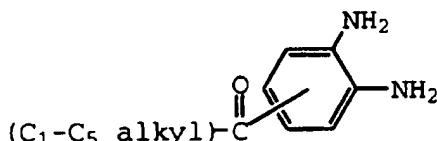
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III

in a solvent or solvent mixture. It is generally preferred that the solvent or solvent mixture be heated, preferably to the boiling point of the solvent. Suitable solvents include ethanol, isopropanol, glacial acetic acid, benzene, toluene, chlorobenzene, glycol, ethylene glycol, dimethyl ether, diethyl ether, dimethylformamide, chloroform, ethyl acetate, and the like. It is generally preferred to add a condensation agent such as phosphorous oxychloride, thionyl chloride, p-toluenesulfonic acid, hydrochloric acid, sulfuric acid, phosphoric acid, polyphosphoric acid, phosphorous pentoxide, methanesulfonyl hydroxide, methanesulfonyl chloride, and the like. The cyclization reaction may also optionally be performed in the presence of a base such as sodium hydroxide, sodium mesylate, or potassium tert-butyrate.

In those compounds in which R² is phenyl a derivative of N-phenyl-o-phenylenediamine was used as the starting material for the cyclization reaction. The examples *infra* provide sufficient guidance in the preparation of those compounds of Formula I wherein R³ is hydrogen.

Those compounds of Formula I wherein R³ is not hydrogen, can be prepared by methods taught in the literature. For example, the compounds of this invention wherein R³ is C₂-C₆ alkanoyl can be prepared from the appropriate keto o-phenylenediamine of the formula



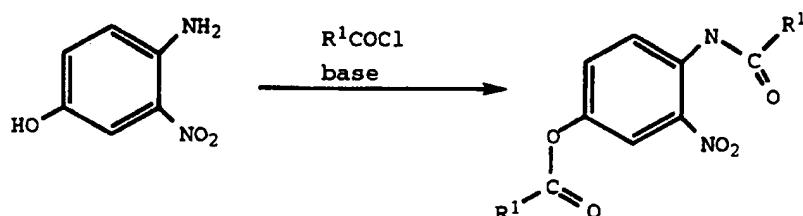
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by methods known in the benzimidazole art such as the procedures described in U.S. Patent 4,401,817, issued August 30, 1983, which is herein incorporated by reference. The method of preparation involves the ammonolysis and reduction of a 4-halo-3-nitrophenyl ketone which is prepared by the Friedel-Crafts reaction of either a 4-halo-3-nitrobenzoyl chloride with an appropriate hydrocarbon or a halobenzene with an appropriate acid chloride followed by aromatic nitration.

Alternatively, the keto benzimidazole reactants can be prepared from acetanilide by a Friedel-Crafts acylation with the appropriate derivative of C₂-C₆ alcanoic acid. The resulting 4-keto acetanilide is nitrated to give a 2-nitro-4-ketoacetanilide. The acetanilide is hydrolyzed to give a 2-nitro-4-ketoaniline, which can then be catalytically hydrogenated to yield a 4-keto-o-phenylenediamine which can then be ring closed to provide the 5 or 6-substituted benzimidazole.

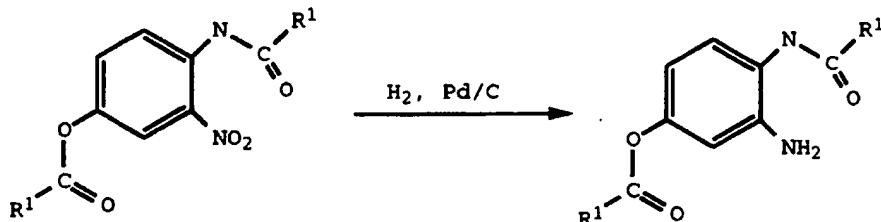
Those compounds of Formula III wherein R³ is a substituted alkyl or alkylidanyl may be prepared by means of a Friedel-Crafts alkylation with the appropriate derivative of the R³ moiety using standard procedures, usually employing an alkyl halide or an olefin in the presence of a catalyst such as aluminum chloride, aluminum bromide or another Lewis acid.

An alternative strategy for preparing those compounds of Formula I wherein R³ is C₁-C₆ alkoxy, R⁴R⁵N-(C₁-C₆ alkoxy)-, or heterocyclic-(C₁-C₆ alkoxy)-, or a substituted derivative thereof, involves first reacting a 3-nitro-4-aminophenol with an acyl halide in the presence of a base



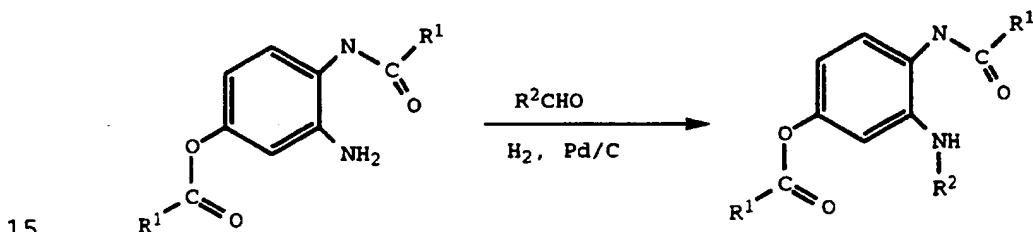
to get substitution of the primary amine as well as substitution of the hydroxy group, the ester moiety serving as a hydroxy-protecting group for subsequent reactions. In the next step of this synthesis the nitro

group is then reduced to an amino group, usually by catalytic hydrogenation.



5

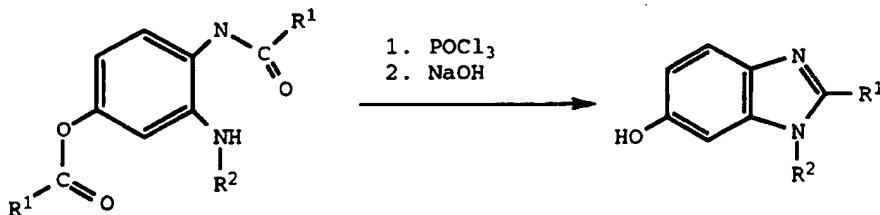
The primary amine of the above compound is then substituted, usually using an aldehyde, such as benzaldehyde or a substituted derivative thereof, followed by hydrogenation, if necessary. In an alternative embodiment, those compounds of Formula I in which 10 R² is alkyl or substituted alkyl may be produced by alkylation of an aromatic amine with alkyl halide or tosylate, or the like, in the presence of a suitable base, such as trialkylamine, potassium carbonate, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and the like.



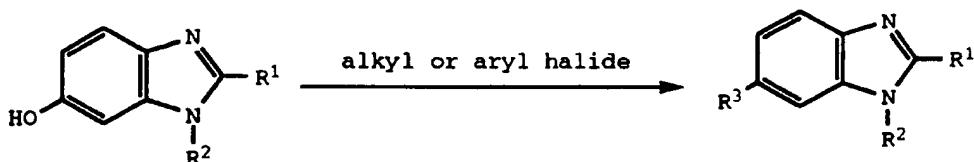
15

Cyclization of this substituted phenylenediamine is then performed as described *supra*, followed by cleavage of the ester group protecting the hydroxy group at the 6-position of the benzimidazole. Suitable 20 cyclization catalysts include phosphorous oxychloride, thionyl chloride, phosphorous pentoxide, phosphorous pentachloride, and other like strong dehydrating agents.

- 15 -



5 A preferred method of cleaving this ester is by incubation of the intermediate in a basic solution, such as 1N sodium hydroxide, or a weaker base such as potassium carbonate. The hydroxy group at the 6-position is then substituted using an alkyl or aryl halide, resulting in a compound of Formula I.



10

The skilled artisan understands that compounds of Formula I substituted at the 5-position of the benzimidazole can be prepared as described above by employing 3-amino-4-nitrophenol as the starting material instead of the 3-nitro-4-aminophenol shown *supra*.

15

Those compounds of Formula I wherein R^2 is alkyl or substituted alkyl may alternatively be prepared by the direct alkylation of a benzimidazole wherein the nitrogen at the 1-position is substituted with a hydrogen. This type of alkylation is usually performed by the reaction of the benzimidazole with an alkyl halide in the presence of a strong base, such as sodium hydride. This reaction is usually performed in a polar aprotic solvent, such as N,N -dimethylformamide, dimethyl sulfoxide, dimethylacetamide, hexamethylphosphoric triamide, and the like.

20

25 The following examples further illustrate the preparation of the compounds of Formula I. The examples are illustrative only and are not intended to limit the scope of the invention in any way. The designations "NMR", "IR", and "MS" in an example indicate that the nuclear magnetic resonance spectrum (NMR), the infrared absorption

spectrum (IR), or the mass as determined by mass spectrometry (MS) were consistent with the desired compound.

Example 1

5

Synthesis of 1,2-diphenylbenzimidazole

N-phenyl-o-phenylenediamine (10 mmol, 1.84 grams) was added to diethyl ether (100 ml) and stirred at room temperature as benzoyl chloride (10 mmol, 1.41 g) was added dropwise (a precipitate 10 formed after about one half of the benzoyl chloride was added). After addition of the benzoyl chloride, the solution was stirred at room temperature for about 15 minutes. The reaction mixture was partitioned between aqueous sodium hydroxide and diethyl ether. The organic layer was removed and the aqueous layer was extracted with 15 ethyl acetate (3 x 100 ml). The organic fractions were combined and dried over magnesium sulfate. The magnesium sulfate was filtered out and the solvent removed in vacuo to yield a red/brown solid (2.88 g, 99.8%) which was suitable for use in the cyclization reaction. NMR, mp 136-137°C.

20

A solution of the intermediate synthesized supra (2.5 g, 8.6 mmol) and phosphorous pentoxide/methanesulfonyl chloride (1:10) (30 ml) was heated at 100°C for about one hour. The reaction mixture was then stirred with ice as 5N sodium hydroxide was added to raise the pH 25 to 14. This mixture was then partitioned with ethyl acetate in a separation funnel. The ethyl acetate layer was removed and the aqueous layer was washed with ethyl acetate (3 x 100 ml). The organic layers were combined and dried over potassium carbonate overnight. The solution was filtered and the solvent removed in vacuo to yield 2.2 grams (94.6%) of crude product.

30

The product was purified by chromatography using a hexanes/ethyl acetate (4:1) solution as the eluent to yield 1.98 grams (85.2%) of the pure title product. NMR, MS 271(M⁺), mp 108-110°C.

Analysis for C₁₉H₁₄N₂:

Theory: C, 84.42; H, 5.22; N, 10.36.

35

Found: C, 84.72; H, 5.27; N, 10.35.

Example 2**Synthesis of 1-phenyl-2-(4-methoxyphenyl)benzimidazole**

5 A solution of N-phenyl-o-phenylenediamine (10 mmol, 1.84 g) in 100 ml diethyl ether was stirred at room temperature as p-anisoyl chloride (1 mmol, 1.71 g) was added dropwise. The resulting mixture was stirred at room temperature for about 96 hours. A precipitate formed before half of the anisoyl chloride/diethyl ether was added.

10 The resulting reaction mixture was partitioned with 1N sodium hydroxide and the organic layer separated. The aqueous layer was extracted with ethyl acetate (3 x 100 ml). The organic layers were combined and dried over potassium carbonate overnight, filtered, and the solvents were removed in vacuo. This yielded 3.57 grams of a dark brown crude product. Further purification could be performed by way of 15 recrystallization from methylene chloride to yield a homogenous spot as determined by chromatography. mp 147-149°C.

20 A solution of the intermediate prepared *supra* (3.19 g, 10 mmol) in 35 ml phosphorous pentoxide/methanesulfonyl chloride (1:10) was stirred at 100°C for about 2.5 hours. The resulting reaction mixture 25 was poured over ice and stirred as aqueous sodium hydroxide was added. The final solution had a pH of 14. This solution was partitioned with ethyl acetate. The ethyl acetate layer was removed and the aqueous layer was extracted with ethyl acetate (3 x 100 ml). The organic layers were combined and washed with saturated sodium chloride. This was then dried over potassium carbonate, filtered, concentrated in vacuo to yield a brown/dark red crude product.

30 This crude product was purified by chromatography using hexanes/ethyl acetate (9:1) as eluent to yield 1.38 grams of the title product. NMR, MS 301(M⁺), mp 105-107°C.
Analysis for C₂₀H₁₆N₂O:

Theory: C, 79.98; H, 5.37; N, 9.33.

Found: C, 79.77; H, 5.38; N, 9.11.

Example 3

35

Synthesis of 1-phenyl-2-phenylmethylbenzimidazole

The title intermediate was synthesized in substantial accordance with Journal of Medicinal Chemistry, 18:319 (1975). A solution of N-phenyl-o-phenylenediamine (10 mmol, 1.84 g) and 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (12 mmol, 2.97 g) was stirred in 5 methylene chloride (60 ml) at room temperature. Phenylacetic acid (10 mmol, 1.36 g) in methylene chloride (30 ml) was added via dropping funnel and stirred at room temperature over a drying tube overnight. The resulting reaction mixture was partitioned with 6N sodium hydroxide. The methylene chloride layer was removed and the aqueous 10 layer was extracted with ethyl acetate (3 x 100). The organic fractions were combined, dried over potassium carbonate, filtered and the solvents were removed in vacuo to yield 5.28 grams of a dark red/brown crude product.

The crude product was recrystallized from ethyl acetate and 15 then diethyl ether to yield a white crystalline product (1.77 g, 58.5%) of the title product. mp 108-110°C.

A portion of the intermediate synthesized supra (1.35 g, 4.5 mmol) and 30 ml of phosphorous pentoxide/methane sulfonyl hydroxide (1:10) were stirred at 100°C for about 6 hours. The resulting reaction 20 mixture was poured over ice and neutralized with aqueous sodium hydroxide (to pH 14). The aqueous layer was partitioned with ethyl acetate and separated. The aqueous layer was extracted with ethyl acetate (4 x 200 ml). The organic layers were combined, dried over potassium carbonate, and filtered. The solvent was removed in vacuo 25 and the crude dark red/brown product was purified by chromatography using hexanes/ethyl acetate (9:1) as the eluent. MS 285(M⁺), mp 106-108°C

Analysis for C₂₀H₁₆N₂O:

Theory: C, 84.48; H, 5.67; N, 9.85.
30 Found: C, 84.75; H, 5.78; N, 9.93.

Example 4

Synthesis of 1-phenyl-2-(3-chlorophenyl)benzimidazole
35 A solution of N-phenyl-o-phenylenediamine (1.84 g, 10 mmol) in diethyl ether (80 ml) was stirred at room temperature as 3-

chlorobenzoylchloride (1.95 g, 11 mmol) in diethyl ether (30 ml) was added dropwise. Precipitate formed almost immediately after total addition of the 3-chlorobenzoylchloride. The resulting reaction mixture was stirred at room temperature for about 3 hours.

5 The reaction mixture was partitioned with aqueous sodium hydroxide. The organic layer was removed and the aqueous layer was extracted with ethyl acetate (3 x 120 ml). The organic layers were combined, dried over potassium carbonate, and filtered. The solvent was removed in vacuo to yield 3.5 grams of the desired intermediate.

10 Further purification could be performed using thin layer chromatography with hexanes/ethyl acetate (9:1) as the eluent. mp 133-134°C, NMR.

15 A solution of the intermediate prepared *supra* (2.50 g, 7.7 mmol) and 40 ml phosphorous pentoxide/methane sulfonyl hydroxide (1:10) was stirred at 100°C for about 16 hours. This reaction mixture was then poured over ice and alkalinized with 5N sodium hydroxide (until pH = 14). This aqueous solution was then extracted with ethyl acetate (5 x 150 ml). The organic layers were combined and dried over potassium carbonate, filtered, and concentrated in vacuo to yield 2.2 grams of crude 20 red/brown product.

This crude product was further purified by chromatography using a hexanes/ethyl acetate (9:1) solution as the eluent. MS 305, 307, mp 107-109°C.

Analysis for C₁₉H₁₃ClN₂:

25 Theory: C, 74.88; H, 4.30; N, 9.19.

Found: C, 74.68; H, 4.47; N, 9.25.

Example 5

30 **Synthesis of 1-phenyl-2-(4-chlorophenyl)benzimidazole**

A solution of N-phenyl-o-phenylenediamine (1.84 g, 10 mmol) in diethyl ether (80 ml) was stirred at room temperature as 4-chlorobenzoylchloride (1.95 g, 11 mmol) in diethyl ether (30 ml) was added dropwise. Precipitate formed almost immediately after total addition of the 4-chlorobenzoylchloride. After total addition of the 4-

- 20 -

chlorobenzoylchloride, the resulting reaction mixture was stirred at room temperature for about 17 hours.

The reaction mixture was partitioned with 1N sodium hydroxide. The diethyl ether layer was removed and the aqueous layer 5 extracted with ethyl acetate (4 x 150 ml). The organic layers were combined, dried over potassium carbonate, filtered, and concentrated in vacuo to yield 3.72 grams (>99%) of a dark red/brown solid. The crude product could be used as is or could be further purified. In the further 10 purification the crude product was triturated in diethyl ether and filtered to yield an off-white solid. mp 169-171°C.

A portion of the intermediate synthesized above (crude, 2.84 g) was stirred in phosphorous pentoxide/methanesulfonyl hydroxide (1:10, 40 ml) at 100°C for about 16 hours. The reaction mixture was 15 poured over ice and alkalized with 5N sodium hydroxide (pH=14). The aqueous layer was extracted with ethyl acetate (5 x 150 ml). The combined organic fractions were dried over potassium carbonate, filtered, and concentrated in vacuo to yield 2.52 grams of crude title product. Further purification could be accomplished by chromatography to yield a solid yellow crystal. MS 305, 307, mp 139- 20 141°C.

Analysis for C₁₉H₁₃ClN₂:

Theory: C, 74.88; H, 4.30; N, 9.19.

Found: C, 74.97; H, 4.33; N, 9.21.

25

Example 6

Synthesis of 1-phenyl-2-(3-methoxyphenyl)benzimidazole

The titled intermediate was prepared essentially as described in Journal of Medicinal Chemistry, 18:319 (1975). A solution of 30 N-phenyl-o-phenylenediamine (1.84 g, 10 mmol) and m-methoxybenzoic acid (1.52 g, 10 mmol) was stirred at room temperature in methylene chloride (80 ml). N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (2.97 g) was added dropwise and the reaction was refluxed for about 16 hours. Additional N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline was added 35 and the reaction was refluxed for an additional 18 hours.

5 The reaction mixture was partitioned with 1N sodium hydroxide. The organic layer (pH ~ 14) was extracted with ethyl acetate (3 x 150 ml). The combined organic fractions were dried over potassium carbonate, filtered and concentrated in vacuo. Crude red oil was
10 purified by chromatography using hexanes/ethyl acetate (9:1) as the eluent. White solid crystallized out of several fractions. mp 118-120°C.

10 A solution of the intermediate prepared above (1.08 g, 3.4 mmol) in chloroform (85 ml) was stirred at room temperature as phosphorous oxychloride (0.52 g, 3.4 mmol) in chloroform (35 ml) was added dropwise. The reaction mixture was then refluxed overnight.

15 The reaction mixture was partitioned with 1N sodium hydroxide. The organic layer was removed and the aqueous layer was extracted with chloroform (3 x 150 ml). The organic layers were combined, washed with a saturated sodium chloride solution, dried over potassium carbonate, filtered and the solvents were removed in vacuo to yield 1.18 grams (>99%).

20 The reaction product was further purified by chromatography using a hexanes/ethyl acetate (9:1) solution as eluent. MS 301(M⁺), mp 110-111°C.

20 Analysis for C₂₀H₁₆N₂O:

Theory: C, 79.98; H, 5.37; N, 9.33.

Found: C, 79.72; H, 5.49; N, 9.39.

Example 7

25 Synthesis of 1-phenyl-2-(4-nitrophenyl)benzimidazole
1-phenylamine-2-[(4-nitrophenyl)carbonylamino]benzene
30 A solution of N-phenyl-o-phenylenediamine (1.84 g, 10 mmol) in diethyl ether (75 ml) was stirred at room temperature as 4-nitrobenzoylchloride (1.86 g, 10 mmol) in diethyl ether (40 ml) was added dropwise. A precipitate quickly formed. The reaction was stirred overnight.

35 The reaction mixture was partitioned with 1 N sodium hydroxide and the organic layer removed. The aqueous layer (pH ~ 14) was extracted with ethyl acetate (3 x 100 ml). The organic layers were

combined, washed with saturated sodium chloride, dried over potassium carbonate, filtered and concentrated in vacuo.

5 The resulting crude product was triturated with diethyl ether and filtered to yield 2.48 grams of an orange/brown product was homogenous by chromatography. mp 169-171°C.

10 A solution of the above-prepared intermediate (2.48 g, 7.4 mmol) in chloroform (80 ml) was stirred at room temperature as phosphorous oxychloride (1.13 g, 7.4 mmol) in chloroform (35 ml) was added dropwise. After constant addition the reaction mixture was refluxed overnight.

15 The reaction mixture was cooled and partitioned with 1 N sodium hydroxide (pH ~ 14). The organic layer was separated and the aqueous layer was extracted with chloroform (3 x 100 ml). The organic layers were combined, washed with saturated sodium chloride solution, dried over potassium carbonate, filtered, and the solvents were removed in vacuo to yield 2.50 grams of a yellow/green solid. The reaction product was purified by chromatography using a hexanes/ethyl acetate (4:1) solution as eluent. MS 316(M⁺), mp 175-177°C.

Analysis for C₁₉H₁₃N₃O₂:

20 Theory: C, 72.37; H, 4.15; N, 13.33.
Found: C, 72.67; H, 4.16; N, 13.30.

Example 8

25 Synthesis of 1-(4-chlorophenyl)-2-phenylbenzimidazole

A solution of N-(4-chlorophenyl)-1,2-phenylenediamine (2.19 g, 10 mmol) in diethyl ether (75 ml) was stirred at room temperature as benzoyl chloride (1.41 g, 10 mmol) in diethyl ether (30 ml) was added dropwise. A precipitate quickly formed. The reaction mixture was stirred overnight and partitioned with 1N sodium hydroxide.

30 The organic layer was removed and the aqueous layer (pH ~ 14) was extracted with ethyl acetate (3 x 150 ml). The organic layers were combined, washed with saturated sodium chloride, dried over potassium carbonate, filtered and removed in vacuo. The crude product 35 was triturated in diethyl ether to yield 1.84 grams (57%) of a white solid which was chromatographically homogenous. mp 158-160°C.

5 A solution of the intermediate prepared *supra* (.33 g, 7.2 mmol) in chloroform (80 ml) was stirred at room temperature as phosphorous oxychloride (1.10 g, 7.2 mmol) in chloroform (30 ml) was added dropwise. After the addition was complete the reaction mixture was refluxed overnight. The reaction mixture was alkalized to pH = 14 with 1N sodium hydroxide and separated.

10 The aqueous layer was extracted with chloroform (3 x 10 ml). The organic layers were combined, washed with a saturated sodium chloride, dried over potassium carbonate, filtered, and the solvents were removed in vacuo to yield 2.45 grams of a red/brown oil which solidified upon setting at room temperature. The product was purified by chromatography using a hexanes/ethyl acetate (4:1) as eluent. MS 305, 307, mp 122-123°C.

15 Analysis for C₁₉H₁₃ClN₂:

Theory: C, 74.88; H, 4.30; N, 9.19.

Found: C, 75.18; H, 4.30; N, 9.15.

Example 9

20 Synthesis of 1-phenyl-2-(3-trifluoromethylphenyl)-benzimidazole

A solution of N-phenyl-o-phenylenediamine (1.84 g, 10 mmol) in diethyl ether (80 ml) was stirred at room temperature as m-trifluoromethylbenzoyl chloride (2.09 g, 10 mmol) in diethyl ether (30 ml) was added dropwise. The reaction mixture was stirred overnight.

25 The reaction mixture was partitioned with 1N sodium hydroxide (pH ~ 14) and the organic layer removed. The aqueous layer was extracted with ethyl acetate (3 x 100 ml). The organic layers were combined, washed with a saturated sodium chloride solution, dried over potassium carbonate, filtered, and the solvents were removed in vacuo to 30 yield a dark red/brown oil which solidified upon standing at room temperature. The reaction product was purified by chromatography using a hexanes/ethyl acetate (4:1) solution as eluent.

A solution of the intermediate prepared above (3.20 g, 9.0 mmol) in chloroform (85 ml) was stirred at room temperature as 35 phosphorous oxychloride (1.78 g, 9 mmol) in chloroform (35 ml) was added dropwise. The reaction mixture was refluxed overnight.

5 The reaction mixture was partitioned with 1N sodium hydroxide. The organic layer was removed and the aqueous layer was extracted with chloroform (3 x 150 ml). The organic layers were combined, washed with a saturated sodium chloride solution, dried over potassium carbonate, filtered, and the solvents were removed in vacuo to yield 3.00 grams of a yellow/brown oil which solidified upon standing.

10 The reaction product was further purified by chromatography using a hexanes/ethyl acetate (9:1 to 4:1) solution as eluent, yielding 1.89 grams (62%) of a light yellow solid. MS 339(M⁺), mp 99-101°C.

15 Analysis for C₂₀H₁₃F₃N₂:

Theory: C, 71.00; H, 3.87; N, 8.28.

Found: C, 71.21; H, 4.07; N, 8.42.

15

Example 10

Synthesis of 1-phenyl-2-(3-nitrophenyl)benzimidazole

20 A solution of N-phenyl-o-phenylenediamine (1.84 g, 10 mmol) in diethyl ether (80 ml) was stirred at room temperature as 3-nitrobenzoyl chloride (1.86 g, 10 mmol) in diethyl ether (30 ml) was added dropwise. The reaction mixture was stirred overnight at room temperature.

25 The reaction mixture was partitioned with 1N sodium hydroxide. The organic layer was removed and the aqueous layer was extracted with ethyl acetate (3 x 100 ml). The organic layers were combined, washed with a saturated sodium chloride solution, dried over potassium carbonate, filtered, and the solvents were removed in vacuo.

The product was purified by trituration with diethyl ether to yield 2.19 g (65.7%) of a yellow solid. mp 127-129°C.

30 A solution of the intermediate prepared above (2.9 g, 8.7 mmol) in chloroform (85 ml) was stirred at room temperature was phosphorous oxychloride (in 35 ml chloroform) was added dropwise. The reaction mixture was then refluxed overnight.

35 The reaction mixture was partitioned with 1N sodium hydroxide and the organic layer was removed. The aqueous layer was extracted with chloroform (3 x 120 ml). The organic fractions were

combined, washed with a saturated sodium chloride solution, dried over potassium carbonate, filtered, and the solvents were removed in vacuo to yield 2.50 grams of a brown/green solid.

5 The reaction product was further purified using thin layer chromatography with a hexanes/ethyl acetate (9:1 to 4:1) solution as eluent. MS 316(M⁺), mp 166-168°C.

Analysis for C₁₉H₁₃N₃O₂:

Theory: C, 72.37; H, 4.16; N, 13.33.

Found: C, 72.54; H, 4.27; N, 13.55.

10

Example 11

Synthesis of 1-(4-chlorophenyl)-2-(4-chlorophenyl)-benzimidazole

15 A solution of N-(4-chlorophenyl)-1,2-phenylenediamine (2.19 g, 10 mmol) in diethyl ether (85 ml) was stirred at room temperature as 4-chlorobenzoyl chloride (1.75 g, 10 mmol) in diethyl ether (35 ml) was added dropwise. The reaction mixture was stirred overnight at room temperature.

20 The reaction mixture was partitioned with 1N sodium hydroxide. The organic layer was removed and the aqueous layer (pH ~ 14) was extracted with ethyl acetate (3 x 100 ml). The organic fractions were combined, washed with a saturated sodium chloride solution, dried over potassium carbonate, filtered, and the solvents were removed in vacuo to yield a crude red/brown solid.

25 The reaction product was purified by trituration with diethyl ether to yield 2.91 grams (81.5%) of an off-white solid which was chromatographically homogeneous. mp 180-181°C.

30 A solution of the intermediate prepared above (3.16 g, 8.8 mmol) in chloroform (90 ml) was stirred at room temperature as phosphorous oxychloride (1.36 g, 8.8 mmol) in chloroform (35 ml) was added dropwise. The reaction mixture was then refluxed overnight.

35 The mixture was partitioned with 1N sodium hydroxide and the organic layer was removed. The aqueous fraction was extracted with chloroform (3 x 150 ml). The organic layers were combined, washed with a saturated sodium chloride solution, dried over potassium

carbonate, filtered, and the solvents were removed in vacuo to yield 2.83 grams of a gray/brown solid.

The reaction product was further purified by chromatography to yield 2.31 grams (77%) of a light pink solid. MS 339, 5 341, mp 162-164°C.

Analysis for C₁₉H₁₂Cl₂N₂:

Theory: C, 67.27; H, 3.57; N, 8.30.

Found: C, 67.45; H, 3.72; N, 8.36.

10

Example 12

Synthesis of 1-phenyl-2-(4-trifluoromethylphenyl)-benzimidazole

A solution of N-phenyl-o-phenylenediamine (1.84 g, 10 mmol) in diethyl ether (85 ml) was stirred at room temperature as 4-(trifluoromethyl)benzoyl chloride (2.09 g, 10 mmol) in diethyl ether (30 ml) was added dropwise. The reaction mixture was stirred overnight at room temperature.

The reaction mixture was partitioned with 1N sodium hydroxide. The organic layer was removed and the aqueous layer extracted with ethyl acetate (3 x 100 ml). The organic layers were combined, washed with a sodium chloride solution, dried over potassium carbonate, filtered, and the solvents were removed in vacuo to yield a brown/black solid.

The crude product was triturated with diethyl ether and vacuum filtered to yield 2.56 grams (72%) of a yellow solid which was homogeneous on thin layer chromatography. mp 143-145°C.

A solution of the intermediate prepared above (3.25 g, 9.1 mmol) in chloroform (85 ml) was stirred at room temperature as phosphorous oxychloride in chloroform (35 ml) was added dropwise. 30 The reaction mixture was partitioned with 1N sodium hydroxide.

The organic layer was removed and the aqueous layer was extracted with chloroform (3 x 150 ml). The organic layers were combined, washed with a saturated sodium chloride solution, dried over potassium carbonate, filtered, and the solvents were removed in vacuo to 35 yield a red/brown oil which solidified upon standing.

The reaction product was further purified by chromatography using a hexanes/ethyl acetate (9:1 to 4:1) solution as eluent. Yield: 2.39 grams (77.6%) of a light yellow solid. MS 339(M⁺), mp 133-135°C.

5 Analysis for C₂₀H₁₃F₃N₂:

Theory: C, 71.00; H, 3.87; N, 8.28.

Found: C, 71.28; H, 3.99; N, 8.46.

Example 13

10

Synthesis of 1-phenyl-2-(2-naphthyl)benzimidazole

A solution of N-phenyl-o-phenylenediamine (1.84 g, 10 mmol) was stirred at room temperature in diethyl ether (85 ml) as naphthoyl chloride (10 mmol, 1.91 g) in diethyl ether (35 ml) was added 15 dropwise. The reaction mixture was stirred overnight at room temperature.

The reaction mixture was alkalinized with 1N sodium hydroxide. The organic layer was removed. The aqueous layer (pH ~ 14) was extracted with ethyl acetate (3 x 100 ml). The organic fractions were 20 combined, washed with a saturated sodium chloride solution, dried over potassium carbonate, filtered, and the solvents were removed in vacuo to yield a red/brown solid (3.91 g, >99%).

The solid was triturated with diethyl ether and the remaining solid was collected by vacuum filtration. The reaction 25 product was further purified by chromatography using a hexanes/ethyl acetate (9:1) solution as eluent. mp 147-149°C.

A solution of the intermediate prepared above (2.4 g, 7.1 mmol) in chloroform (85 ml) was stirred at room temperature as phosphorous oxychloride (1.1 g, 7.1 mmol) in chloroform (35 ml) was 30 added dropwise. After the addition the reaction mixture was refluxed overnight.

The reaction mixture was alkalinized with 1N sodium hydroxide. The organic layer was removed and the aqueous layer was extracted with chloroform (3 x 150 ml). The organic layers were 35 combined, washed with a saturated sodium chloride solution, dried over

potassium carbonate, filtered, and the solvents were removed in vacuo to yield 2.38 grams (>99%) of a brown solid.

5 The reaction product was further purified by chromatography using a hexanes/ethyl acetate solution as the eluent to yield 1.91 grams (84%) of a light yellow solid. MS 321(M⁺), mp 169-170°C. Analysis for C₂₃H₁₆N₂:

Theory: C, 86.22; H, 5.03; N, 8.04.

Found: C, 86.21; H, 5.24; N, 8.61.

10

Example 14

Synthesis of 1-phenyl-2-(3,5-dimethoxyphenyl)benzimidazole

15 A solution of N-phenyl-o-phenylenediamine (1.84 g, 10 mmol) in diethyl ether (85 ml) was stirred at room temperature as 3,5-dimethylbenzoyl chloride (2.00 g, 1.84 mmol) in diethyl ether (35 ml) was added dropwise. The reaction mixture was stirred at room temperature overnight.

20 The reaction mixture was alkalinized with 1N sodium hydroxide and the organic layer was removed. The aqueous layer was extracted with ethyl acetate (3 x 100 ml). The organic layers were combined, washed with a saturated sodium chloride solution, dried over potassium carbonate, filtered, and the solvents were removed in vacuo to yield 3.46 grams of a red/brown oil which solidified upon standing.

25 Further purification of the title intermediate was achieved by chromatography. mp 107-109°C.

30 A solution of the crude product of the reaction above (2.3 g, 6.6 mmol) in chloroform (85 ml) was stirred at room temperature as phosphorous oxychloride (1.01 g, 6.6 mmol) in chloroform (25 ml) was added dropwise. The reaction mixture was then refluxed overnight.

35 The reaction mixture was alkalinized with 1N sodium hydroxide. The organic layer was removed and the aqueous layer was extracted with methylene chloride (3 x 100 ml). The organic layers were combined, washed with saturated sodium chloride solution, dried over potassium carbonate, filtered, and the solvents were removed in vacuo to yield a red/brown oil which solidified upon standing.

Further purification of the reaction product was accomplished by chromatography, employing a hexanes/ethyl acetate mixture as the eluent to yield 1.91 grams (87.6%) of a light yellow solid. MS 331(M⁺), mp 98-99°C.

5 Analysis for C₂₁H₁₈N₂O₂:

Theory: C, 76.34; H, 5.49; N, 8.48.

Found: C, 76.17; H, 5.60; N, 8.51.

Example 15

10

Synthesis of 1-phenyl-2-(3,4-dimethoxyphenyl)benzimidazole

A solution of N-phenyl-o-phenylenediamine (1.84 g, 10 mmol) in diethyl ether (85 ml) was stirred at room temperature as 3,4-dimethoxybenzoyl chloride (2.01 g, 10 mmol) in 40 ml of diethyl ether was 15 added dropwise. The reaction mixture was then stirred overnight at room temperature.

The reaction mixture was then alkalized with 1N sodium hydroxide. The organic layer was removed and the aqueous layer was extracted with diethyl ether (3 x 150 ml). The organic fractions were 20 combined, washed with a saturated sodium chloride solution, dried over potassium carbonate, filtered, and the solvents were removed in vacuo to yield 3.11 grams.

This intermediate was further purified by chromatography using a hexanes/ethyl acetate solution as the eluent, followed by 25 trituration with hexanes to yield a white crystalline solid. mp 159-160°C.

A solution of the intermediate prepared *supra* (3.11 g, 8.9 mmol) in chloroform (30 ml) was stirred at room temperature as phosphorous oxychloride (1.40 g, 9 mmol) in chloroform (30 ml) was 30 added dropwise. The reaction mixture was then refluxed overnight. The reaction mixture was partitioned with 1N sodium hydroxide.

The organic fraction was removed and the aqueous phase was extracted with methylene chloride (3 x 150 ml). The organic fractions were combined, washed with saturated sodium chloride solution, dried over potassium carbonate, filtered, and the solvents were 35 removed in vacuo to yield a brown oil which solidified upon standing.

The crude product was partitioned between 1N hydrochloric acid and a hexanes/ethyl acetate (1:1) solution. The aqueous layer was removed and the organic layer was extracted with 1N hydrochloric acid (3 x 100 ml). The aqueous fractions were combined and alkalinized to pH 5 14 with sodium hydroxide. This basified solution was extracted with ethyl acetate (5 x 100 ml). The organic layers were combined, washed with a saturated sodium chloride solution, dried over potassium carbonate, filtered, and the solvents were removed in vacuo to yield 1.70 grams (57.8%) of a pink solid. MS 331(M⁺), mp 114-115°C.

10 Analysis for C₂₁H₁₈N₂O₂:

Theory: C, 76.34; H, 5.49; N, 8.48.

Found: C, 76.31; H, 5.63; N, 8.53.

Example 16

15

Synthesis of 1-phenyl-2-(3,4,5-trimethoxyphenyl)-benzimidazole

A solution of N-phenyl-o-phenylenediamine (1.84 g, 10 mmol) in diethyl ether (90 ml) was stirred at room temperature as 3,4,5-trimethoxybenzoyl chloride (2.31 g, 10 mmol) in diethyl ether (40 ml) was 20 added dropwise. The reaction mixture was then stirred overnight at room temperature. The solvents were then removed in vacuo leaving N-[3,4,5-trimethoxyphenyl]carbonyl]-N'-phenyl-phenylenediamine.

The crude intermediate (3.6 g, 9.5 mmol) in chloroform (100 ml) was stirred at room temperature as phosphorous oxychloride (1.5 g, 25 9.5 mmol) in chloroform (20 ml) was added dropwise. The reaction mixture was then stirred at room temperature for about 72 hours.

The reaction mixture was partitioned between 1N hydrochloric acid and ethyl acetate. The organic phase was discarded and the aqueous phase was alkalinized with 1N sodium hydroxide. The 30 aqueous solution was then extracted with ethyl acetate (3 x 100 ml). The organic fractions were combined and dried over potassium carbonate. The solvents were removed in vacuo to yield the title product as a white solid (2.08 g, 61%). MS 361(M⁺), mp 139-141°C.

Analysis for C₂₂H₂₀N₂O₃:

35 Theory: C, 73.32; H, 5.59; N, 7.77.

Found: C, 73.17; H, 5.71; N, 7.72.

Example 17**Synthesis of 1-(4-chlorophenyl)-2-(4-methoxyphenyl)-benzimidazole**

5 A solution of N-(4-chlorophenyl)-1,2-phenylenediamine (2.13 g, 10 mmol) in diethyl ether (90 ml) was stirred at room temperature as p-anisoyl chloride (1.71 g, 10 mmol) in diethyl ether (45 ml) was added dropwise. The mixture was stirred overnight at room temperature.

10 The reaction mixture was partitioned with 1N sodium hydroxide. The organic layer was removed and the aqueous fraction was extracted with ethyl acetate (3 x 150 ml). The organic layers were combined, washed with a saturated sodium chloride solution, dried over potassium carbonate, filtered, and the solvents were removed in vacuo to yield 3.6 grams of a brown/pink solid.

15 The desired intermediate was further purified by chromatography using a hexanes/ethyl acetate (3:1) solution as the eluent to yield a light pink solid. mp 162-164°C.

20 The intermediate prepared above (3.40 grams, 9.6 mmol) was dissolved in chloroform (90 ml). This solution was stirred at room temperature as phosphorous oxychloride in chloroform (40 ml) was added dropwise. The reaction mixture was refluxed overnight.

25 The reaction mixture was partitioned with 1N sodium hydroxide and the organic layer removed. The aqueous fraction was further extracted with methylene chloride (3 x 150 ml). The organic layers were combined, washed with a saturated sodium chloride solution, dried over potassium carbonate, filtered, and the solvents were removed in vacuo.

30 The reaction product was further purified by chromatography to yield 2.64 grams (82.1%) of a light pink solid. MS 335, 337, mp 183-185°C.
Analysis for $C_{20}H_{15}ClN_2O$:

Theory: C, 71.75; H, 4.52; N, 8.37.

Found: C, 71.67; H, 4.77; N, 8.59.

Synthesis of 1-phenyl-2-(4-methylphenyl)benzimidazole

A solution of N-phenyl-o-phenylenediamine (1.84 g, 10 mmol) in diethyl ether (85 ml) was stirred at room temperature as p-toluooyl chloride (1.60 g, 10 mmol) in diethyl ether (35 ml) was added 5 dropwise. The reaction mixture was stirred overnight at room temperature.

The reaction mixture was alkalized with 1N sodium hydroxide. The organic layer was removed and the aqueous fraction was extracted with ethyl acetate (3 x 150 ml). The organic layers were 10 combined, washed with a saturated sodium chloride solution, dried over potassium carbonate, filtered, and the solvents were removed in vacuo to yield 3.18 grams of a red/brown solid.

The intermediate was further purified by chromatography using a hexanes/ethyl acetate (9:1) solution as the eluent to yield a yellow 15 solid. mp 143-145°C.

The intermediate prepared above (2.63 g, 8.6 mmol) was dissolved in chloroform (85 ml). This solution was stirred at room temperature as phosphorous oxychloride (1.35 g, 8.6 mmol) in chloroform (30 ml) was added dropwise. The reaction mixture was 20 refluxed overnight.

The reaction mixture was partitioned with 1N sodium hydroxide and the organic layer removed. The aqueous layer was extracted with methylene chloride (3 x 150 ml). The organic fractions were combined, washed with a saturated sodium chloride solution, 25 dried over potassium carbonate, filtered and the solvents were removed in vacuo to yield a red/brown oil which solidified upon standing.

The reaction product was further purified by chromatography using a hexanes/ethyl acetate (4:1) solution as the eluent. The fractions were combined, the solvents removed in vacuo and 30 the resulting oil was triturated with diethyl ether. The title product was recrystallized from diethyl ether/hexanes to yield 1.54 grams (63%). MS 285(M⁺)

Analysis for C₂₀H₁₆N₂:

Theory: C, 84.48; H, 5.67; N, 9.85.
35 Found: C, 85.60; H, 5.94; N, 10.45.

Example 19**Synthesis of 1-phenyl-2-(3-methylphenyl)benzimidazole**

5 A solution of N-phenyl-o-phenylenediamine (1.84 g, 10 mmol) in diethyl ether (90 ml) was stirred at room temperature as m-toluoyl chloride (1.55, 10 mmol) in diethyl ether (30 ml) was added dropwise. The reaction mixture was stirred at room temperature overnight.

10 The reaction mixture was then alkalinized with 1N sodium hydroxide. The organic layer was removed and the aqueous fraction was extracted with ethyl acetate (3 x 150 ml). The organic fractions were combined, washed with a saturated sodium chloride solution, dried over potassium carbonate, filtered, and the solvents were removed in vacuo to yield 3.12 grams of a gray/brown solid.

15 The intermediate was further purified by chromatography. mp 129-130°C.

20 The intermediate prepared above (2.5 g, 8.3 mmol) in chloroform (95 ml) was stirred at room temperature as phosphorous oxychloride (1.30 g, 8.4 mmol) in chloroform (30 ml) was added dropwise. The reaction mixture was refluxed overnight.

25 The reaction mixture was alkalinized with 1N sodium hydroxide and the organic layer was removed. The aqueous layer was extracted with methylene chloride (3 x 150 ml). The organic layers were combined, washed with a saturated sodium chloride solution, dried over potassium carbonate, filtered, and the solvents were removed in vacuo.

30 The reaction product was further purified by chromatography using a hexanes/ethyl acetate (4:1) solution as eluent. The product was recrystallized from hexanes to yield 0.97 grams (41.1%) of a white solid. MS 285(M⁺), mp 69-71°C.

Analysis for C₂₀H₁₆N₂:

Theory: C, 84.48; H, 5.67; N, 9.85.

Found: C, 84.48; H, 5.72; N, 9.80.

Example 20**Synthesis of 1-phenyl-2-(4-cyanophenyl)benzimidazole**

A solution of N-phenyl-o-phenylenediamine (1.84 g, 10 mmol) in diethyl ether (100 ml) was stirred at room temperature as 4-cyanobenzoyl chloride (1.66 g, 10 mmol) in diethyl ether (40 ml) was added dropwise. The reaction mixture was stirred overnight at room 5 temperature.

The reaction mixture was partitioned with 1N sodium hydroxide. The organic fraction was removed and the aqueous layer was extracted with ethyl acetate (3 x 150 ml). The combined organic layers were washed with a saturated sodium chloride solution, dried 10 over potassium carbonate, filtered and the solvents were removed in vacuo to yield 3.31 grams of a red/black oily gum.

This oily gum (2.8 g, 8.9 mmol) was dissolved in chloroform (90 ml). This solution was stirred as phosphorous oxychloride (1.40 g, 9.0 mmol) in chloroform (35 ml) was added dropwise. This reaction 15 mixture was refluxed overnight.

The reaction mixture was alkalinized with 1N sodium hydroxide. The organic layer was removed and the aqueous fraction was extracted with methylene chloride (3 x 150 ml). The organic layers were combined, washed with a saturated sodium chloride solution, dried 20 over potassium carbonate, filtered, and the solvents were removed in vacuo to yield a red/brown oil.

The reaction product was further purified by chromatography using a hexanes/ethyl acetate solution as eluent. The title product then was recrystallized from ethyl acetate to yield a white 25 solid. MS 296(M⁺), mp 182-184°C.

Analysis for C₂₀H₁₃N₃:

Theory: C, 81.34; H, 4.44; N, 14.23.

Found: C, 81.55; H, 4.50; N, 14.47.

30

Example 21

Synthesis of 1-phenyl-2-cyclohexylbenzimidazole

A solution of N-phenyl-o-phenylenediamine (1.84 g, 10 mmol) in diethyl ether (85 ml) was stirred at room temperature as 35 cyclohexanecarbonyl chloride (1.46 grams, 10 mmol) in diethyl ether (3

ml) was added dropwise. The reaction mixture was stirred at room temperature overnight.

The reaction mixture was alkalinized with 1N sodium hydroxide. The organic fraction was removed and the aqueous phase 5 was extracted with ethyl acetate (3 x 150 ml). The organic fractions were combined, washed with saturated sodium chloride solution, dried over potassium carbonate, filtered, and the solvents were removed in vacuo to yield 2.81 grams of a brown solid. The reaction product was further purified by chromatography to yield N-phenyl-N'-cyclohexylcarbonyl-10 phenylenediamine as a yellow solid.

The intermediate prepared above (2.0 g, 7 mmol) was dissolved in chloroform (80 ml). This solution was stirred at room temperature as phosphorous oxychloride (1.05 g, 7 mmol) in chloroform (30 ml) was added dropwise. The reaction mixture was refluxed 15 overnight.

The reaction mixture was alkalinized with 1N sodium hydroxide. The organic layer was removed and the aqueous layer was extracted with methylene chloride (3 x 150 ml). The organic fractions were combined, washed with a saturated sodium chloride solution, 20 dried over potassium carbonate, filtered, and the solvents were removed in vacuo to yield 2.81 grams of a black/red oil which solidified upon standing.

The reaction product was further purified by partitioning between 1N hydrochloric acid and an ethyl acetate/hexanes (1:1) 25 solution. The aqueous layer was alkalinized to pH 10 using 1N sodium hydroxide. The aqueous fraction was then extracted with ethyl acetate (4 x 250 ml). The organic layers were combined, washed with a saturated sodium chloride solution, dried over potassium carbonate, filtered and the solvents were removed in vacuo to yield 1.47 grams (76%) of a light 30 yellow solid. MS 277(M⁺), mp 99-101°C.

Analysis for C₁₉H₂₀N₂:

Theory: C, 82.57; H, 7.29; N, 10.14.

Found: C, 82.33; H, 7.45; N, 10.21.

Synthesis of 1-phenyl-2-(2-chlorophenyl)benzimidazole

5 A solution of N-phenyl-o-phenylenediamine (1.84 g, 10 mmol) in diethyl ether (85 ml) was stirred at room temperature as 2-chlorobenzoyl chloride (1.76 g, 10 mmol) in diethyl ether (35 ml) was added dropwise. The reaction mixture was stirred overnight at room temperature.

10 The reaction mixture was alkalinized with 1N sodium hydroxide and the organic layer removed. The aqueous phase was extracted with ethyl acetate (3 x 100 ml). The organic fractions were combined, washed with a saturated sodium chloride solution, dried over potassium carbonate, filtered, and the solvents were removed in vacuo to yield 3.2 grams (>99%) of a gray/brown solid.

15 The crude product prepared *supra* (2.7 g, 8.4 mmol) was dissolved in chloroform (95 ml). This solution was stirred at room temperature as phosphorous oxychloride (1.3 g, 8.5 mmol) in chloroform (30 ml) was added dropwise. The reaction mixture was refluxed overnight and then partitioned with 1N sodium hydroxide.

20 The organic layer was removed and the aqueous phase was extracted with methylene chloride (3 x 150 ml). The combined organic layers were washed with a saturated sodium chloride solution, dried over potassium carbonate, filtered, and the solvents were removed in vacuo.

25 The crude product was further purified by chromatography using a hexanes/ethyl acetate (9:1) solution as the eluent. The recovered product was triturated in hexanes and filtered to yield 1.31 grams (51.2%) of a light yellow solid. MS 305, 307, mp 146-148°C.

Analysis for $C_{19}H_{13}ClN_2$:

Theory: C, 74.88; H, 4.30; N, 9.19.

Found: C, 75.16; H, 4.31; N, 9.21.

30

Example 23**Synthesis of 1-phenyl-2-(2-methylphenyl)benzimidazole**

35 A solution of N-phenyl-o-phenylenediamine (1.84 g, 10 mmol) in diethyl ether (90 ml) was stirred at room temperature as o-toluoyl chloride (1.55 g, 10 mmol) in diethyl ether (35 ml) was added

dropwise. The reaction mixture was stirred overnight at room temperature.

5 The reaction mixture was alkalinized with 1N sodium hydroxide and the organic layer was removed. The aqueous fraction was extracted with ethyl acetate (3 x 100 ml). The organic fractions were combined, washed with a saturated sodium chloride solution, dried over potassium carbonate, filtered, and the solvents were removed in vacuo.

10 The reaction product was further purified by chromatography using a hexanes/ethyl acetate (3:1) solution as the eluent. Trituration with hexanes and subsequent filtration yielded a white solid. mp 118-120°C.

15 The intermediate prepared above (2.52 g, 8.3 mmol) in chloroform (95 ml) was stirred at room temperature as phosphorous oxychloride (1.33 g, 8.4 mmol) in chloroform (30 ml) was added dropwise. The reaction mixture was refluxed overnight.

20 The reaction mixture was alkalinized with 1N sodium hydroxide and the organic layer was removed. The aqueous layer was extracted with methylene chloride (3 x 150 ml). The organic layers were combined, washed with a saturated sodium chloride solution, dried over potassium carbonate, filtered, and the solvents were removed in vacuo.

25 The reaction product was further purified by chromatography using a hexanes/ethyl acetate (9:1 to 4:1) solution as the eluent to yield a pale yellow oil. The product was triturated with hexanes to yield a light yellow solid. MS 285(M⁺), mp 99-101°C.

Analysis for C₂₀H₁₆N₂:

Theory: C, 84.48; H, 5.67; N, 9.85.

Found: C, 84.48; H, 5.72; N, 9.80.

Example 24

30

Synthesis of 1-phenyl-2-(2-methoxyphenyl)benzimidazole

A solution of N-phenyl-o-phenylenediamine (1.84 g, 10 mmol) in diethyl ether (90 ml) was stirred at room temperature as 2-methoxybenzoyl chloride (1.55 g, 10 mmol) in diethyl ether (35 ml) was added dropwise. The reaction mixture was stirred overnight at room temperature.

5 The reaction mixture was alkalinized with 1N sodium hydroxide and the organic layer was removed. The aqueous fraction was extracted with ethyl acetate (3 x 100 ml). The organic fractions were combined, washed with a saturated sodium chloride solution, dried over potassium carbonate, filtered, and the solvents were removed in vacuo.

10 The reaction product was further purified by chromatography using a hexanes/ethyl acetate (9:1) solution as eluent. The reaction product was recrystallized from hexanes. mp 178-180°C.

15 The intermediate prepared above (2.65 g, 8.3 mmol) in chloroform (95 ml) was stirred at room temperature as phosphorous oxychloride (1.33 g, 8.4 mmol) in chloroform (30 ml) was added dropwise. The reaction mixture was refluxed overnight.

20 The reaction mixture was alkalinized with 1N sodium hydroxide and the organic layer was removed. The aqueous layer was extracted with methylene chloride (3 x 150 ml). The organic layers were combined, washed with a saturated sodium chloride solution, dried over potassium carbonate, filtered, and the solvents were removed in vacuo.

25 The reaction product was further purified by chromatography using a hexanes/ethyl acetate (4:1) solution as eluent to yield 1.64 grams (65.7%) of the title product as a white solid. MS 301(M⁺), mp 159-160°C.

Analysis for C₂₀H₁₆N₂O:

Theory: C, 79.98; H, 5.37; N, 9.33.

Found: C, 80.01; H, 5.36; N, 9.40.

25

Example 25

Synthesis of 1-phenyl-2-(3-cyanophenyl)benzimidazole

30 A solution of N-phenyl-o-phenylenediamine (1.84 g, 10 mmol) in diethyl ether (90 ml) was stirred at room temperature as 3-cyanobenzoyl chloride (1.66 g, 10 mmol) in diethyl ether (35 ml) was added dropwise. The reaction mixture was stirred overnight at room temperature.

35 The reaction mixture was alkalinized with 1N sodium hydroxide and the organic layer was removed. The aqueous fraction was extracted with ethyl acetate (3 x 100 ml). The organic fractions were

combined, washed with a saturated sodium chloride solution, dried over potassium carbonate, filtered, and the solvents were removed in vacuo.

5 The reaction product was further purified by chromatography using a hexanes/ethyl acetate (4:1) solution as the eluent. The product was recrystallized from hexanes to yield a white solid. mp 141-143°C.

10 The intermediate prepared above (2.63 g, 8.3 mmol) in chloroform (95 ml) was stirred at room temperature as phosphorous oxychloride (1.33 g, 8.4 mmol) in chloroform (30 ml) was added dropwise. The reaction mixture was refluxed overnight.

15 The reaction mixture was alkalinized with 1N sodium hydroxide and the organic layer was removed. The aqueous layer was extracted with methylene chloride (3 x 150 ml). The organic layers were combined, washed with a saturated sodium chloride solution, dried over potassium carbonate, filtered, and the solvents were removed in vacuo.

20 The reaction product was further purified by chromatography using a hexanes/ethyl acetate (9:1 to 4:1) solution as eluent. The title product was recrystallized from hexanes and ethyl acetate. MS 296(M⁺), mp 153-154°C.

Analysis for C₂₀H₁₃N₃:

Theory: C, 81.34; H, 4.44; N, 14.23.

Found: C, 81.60; H, 4.45; N, 14.38.

Example 26

25

Synthesis of 1-dimethylaminoethyl-2-phenylbenzimidazole dihydrochloride

30 A solution of 2-phenylbenzimidazole (0.97 g, 5 mmol) in N,N-dimethylformamide (anhydrous, 20 ml) was stirred at room temperature under nitrogen atmosphere. Two equivalents of sodium hydride in 60% dispersion (0.40 g, 10 mmol) was quickly added and the reaction mixture was allowed to stir under nitrogen. N,N-Dimethylaminoethyl bromide hydrobromide (1.16 g, 5 mmol) in anhydrous N,N-dimethylformamide (12 ml) was added dropwise by 35 syringe to the stirring mixture. The reaction mixture was stirred overnight at room temperature.

- 40 -

The reaction mixture was partitioned between acetic acid and ethyl acetate. The organic layer was discarded and the aqueous phase was extracted with diethyl ether (5 x 75 ml). All organic fractions were discarded.

5 The aqueous phase was alkalized with 2N sodium hydroxide. This solution was then extracted with diethyl ether (4 x 100 ml). The organic fractions were combined, washed with a saturated sodium chloride solution, dried over potassium carbonate, filtered, and the solvents were removed in vacuo to yield 1.11 grams of a cloudy oil.

10 The crude product was stirred with 2N hydrochloric acid in ethanol. The solvents were removed in vacuo to yield 1.16 (66.8%) grams of the title product as a white solid. MS 309, mp 228-231°C
Analysis for C₁₇H₁₉N₃ • 2 HCl:

Theory: C, 60.36; H, 6.26; N, 12.42.
15 Found: C, 60.09; H, 6.22; N, 12.18.

Example 27

Synthesis of 1-phenyl-2-(3,4-dichlorophenyl)benzimidazole

20 A solution of N-phenyl-o-phenylenediamine (1.84 g, 10 mmol) in diethyl ether (90 ml) was stirred at room temperature as 3,4-dichlorobenzoyl chloride (2.10 g, 10 mmol) in diethyl ether (35 ml) was added dropwise. The reaction mixture was stirred overnight at room temperature.

25 The reaction mixture was alkalized with 1N sodium hydroxide and the organic layer was removed. The aqueous fraction was extracted with ethyl acetate (3 x 100 ml). The organic fractions were combined, washed with a saturated sodium chloride solution, dried over potassium carbonate, filtered, and the solvents were removed in vacuo.

30 The reaction product was further purified by chromatography using a hexanes/ethyl acetate (4:1) solution as the eluent. The product was recrystallized from hexanes to yield a white solid. mp 146-147°C.

35 The intermediate prepared above (3.00 g, 8.4 mmol) in chloroform (95 ml) was stirred at room temperature as phosphorous

oxychloride (1.33 g, 8.4 mmol) in chloroform (30 ml) was added dropwise. The reaction mixture was refluxed overnight.

The reaction mixture was alkalinized with 1N sodium hydroxide and the organic layer was removed. The aqueous layer was 5 extracted with methylene chloride (3 x 150 ml). The organic layers were combined, washed with a saturated sodium chloride solution, dried over potassium carbonate, filtered, and the solvents were removed in vacuo.

The reaction product was further purified by chromatography using a hexanes/ethyl acetate (4:1) solution as eluent. 10 The title product was recrystallized from hexanes and ethyl acetate as a white solid. MS 339, 341, mp 144-146°C.
Analysis for $C_{19}H_{12}Cl_2N_2$:

Theory: C, 67.27; H, 3.57; N, 8.26.

Found: C, 67.53; H, 3.61; N, 8.13.

15

Example 28

Synthesis of 1-(piperidin-1-ylethyl)-2-phenylbenzimidazole dihydrochloride

20 A solution of 2-phenylbenzimidazole (0.97 g, 5 mmol) in N,N-dimethylformamide (anhydrous, 20 ml) was stirred at room temperature under nitrogen atmosphere. Two equivalents of sodium hydride in 60% dispersion (0.40 g, 10 mmol) was quickly added and the reaction mixture was allowed to stir under nitrogen. N-(2-chloroethyl)piperidinyl (10 mmol) in anhydrous N,N-dimethylformamide (12 ml) was added dropwise by syringe to the stirring mixture. The reaction mixture was stirred overnight at room temperature.

30 The reaction mixture was partitioned between acetic acid and ethyl acetate. The organic layer was discarded and the aqueous phase was extracted with diethyl ether (5 x 75 ml). All organic fractions were discarded.

The aqueous phase was alkalinized with 2N sodium hydroxide. This solution was then extracted with diethyl ether (4 x 100 ml). The organic fractions were combined, washed with a saturated

sodium chloride solution, dried over potassium carbonate, filtered, and the solvents were removed in vacuo to yield 1.11 grams of a cloudy oil.

This was then stirred in 2N hydrochloric acid in ethanol. The solvents were removed in vacuo, yielding the crude product, which 5 was recrystallized twice from an ethyl acetate/ethanol solution. The solvents were removed in vacuo to yield 0.95 grams (50.2%) of the title product as a white solid. MS 306
Analysis for $C_{20}H_{23}N_3 \cdot 2 HCl$:

Theory: C, 63.49; H, 6.66; N, 11.11.
10 Found: C, 63.33; H, 6.64; N, 10.92.

Example 29

Synthesis of 1-phenyl-2-(4-hydroxyphenyl)benzimidazole

15 A solution of 1-phenyl-2-(4-methoxyphenyl)benzimidazole(0.60 g, 2.0 mmol) in hydrobromic acid (6 ml) and acetic acid (6 ml) was refluxed for 40 hours. The reaction mixture was extracted with diethyl ether (5 x 150 ml) at a pH of 3-5. The organic solvents were discarded. The aqueous phase was alkalinized to 20 pH 8-9 and extracted with ethyl acetate (5 x 150 ml). The organic fractions were combined and dried over potassium carbonate, then filtered and the solvents were removed in vacuo to yield a white solid. The solid was triturated in diethyl ether and filtered to yield 0.25 grams of the desired product.

25 Analysis for $C_{19}H_{14}N_2O \cdot 0.5 H_2O$:

Theory: C, 77.27; H, 5.12; N, 9.48.
Found: C, 77.56; H, 4.96; N, 9.39.

Example 30

Synthesis of 1-phenyl-2-(3-nitro-4-chlorophenyl)-benzimidazole

30 A solution of N-phenyl-o-phenylenediamine (1.84 g, 10 mmol) and 4-chloro-3-nitro-benzoic acid (2.07 g, 10 mmol) in anhydrous tetrahydrofuran was stirred at room temperature as N-ethoxycarbonyl-35 2-ethoxy-1,2-dihydroquinoline (3.71 g, 15 mmol) in tetrahydrofuran was

added dropwise. The reaction was stirred at room temperature for about 72 hours.

5 The reaction mixture was alkalinized with 1N sodium hydroxide. The aqueous layer was extracted with ethyl acetate (4 x 100 ml). The organic fractions were combined, dried over potassium carbonate, filtered, and the solvents removed in vacuo to yield the crude product.

10 The reaction product was further purified by chromatography using a hexanes/ethyl acetate (4:1) solution as eluent.

15 The intermediate prepared above (3.00 g, 8.4 mmol) in chloroform (95 ml) was stirred at room temperature as phosphorous oxychloride (1.33 g, 8.4 mmol) in chloroform (30 ml) was added dropwise. The reaction mixture was refluxed overnight.

15 The reaction mixture was alkalinized with 1N sodium hydroxide and the organic layer was removed. The aqueous layer was extracted with methylene chloride (3 x 150 ml). The organic layers were combined, washed with a saturated sodium chloride solution, dried over potassium carbonate, filtered, and the solvents were removed in vacuo.

20 The reaction product was further purified by chromatography using a hexanes/ethyl acetate (9:1) solution as eluent. The title product was recrystallized from fractions with ethyl acetate as a white solid. MS 349, 351, mp 179-182°C.

Analysis for C₁₉H₁₂ClN₃O₂:

25 Theory: C, 65.24; H, 3.46; N, 12.01.
Found: C, 65.50; H, 3.51; N, 12.06.

Example 31

30 Synthesis of 1-[2-(morpholin-4-yl)ethyl]-2-phenylbenzimidazole dihydrochloride

35 A solution of 2-phenylbenzimidazole (0.97 g, 5 mmol) in N,N-dimethylformamide (anhydrous, 20 ml) was stirred at 60°C under nitrogen atmosphere. Two equivalents of sodium hydride in 60% dispersion (0.40 g, 10 mmol) was quickly added and the reaction mixture was allowed to stir under nitrogen. N-(2-chloroethyl)morpholine (0.93 g, 5 mmol) in anhydrous N,N-dimethylformamide (12 ml) was added

dropwise by syringe to the stirring mixture. The reaction mixture was stirred overnight at 60°C.

5 The reaction mixture was partitioned between acetic acid and ethyl acetate. The organic layer was discarded and the aqueous phase was extracted with diethyl ether (5 x 75 ml). All organic fractions were discarded.

10 The aqueous phase was alkalinized with 2N sodium hydroxide. This solution was then extracted with diethyl ether (4 x 100 ml). The organic fractions were combined, washed with a saturated sodium chloride solution, dried over potassium carbonate, filtered, and the solvents were removed in vacuo to yield a cloudy oil.

15 The crude product was mixed with a 2N hydrochloric acid/ethanol (1:1) solution. The solvents were removed in vacuo to yield 1.52 grams (40%) of a white solid. MS 308.

15 Analysis for $C_{19}H_{21}N_3O \cdot 2 HCl \cdot EtOH$:

Theory: C, 59.16; H, 6.86; N, 9.85.

Found: C, 59.20; H, 6.85; N, 9.89.

Example 32

20

Synthesis of 1-phenyl-2-propylbenzimidazole

25 A solution of N-phenyl-o-phenylenediamine (1.84 g, 10 mmol) in tetrahydrofuran (90 ml) was stirred at room temperature under a nitrogen atmosphere as butanoyl chloride (1.28 g, 12 mmol) in tetrahydrofuran (35 ml) was added dropwise. The reaction mixture was stirred overnight at room temperature.

30 The reaction mixture was alkalinized with 1N sodium hydroxide and the organic layer was removed. The aqueous fraction was extracted with ethyl acetate (3 x 100 ml). The organic fractions were combined, washed with a saturated sodium chloride solution, dried over potassium carbonate, filtered, and the solvents were removed in vacuo.

35 The reaction product was further purified by chromatography using a hexanes/ethyl acetate (3:1) solution as the eluent. The product was recrystallized from hexanes to yield a white solid.

The intermediate prepared above in chloroform was stirred at room temperature as an equimolar amount of phosphorous oxychloride in chloroform was added dropwise. The reaction mixture was refluxed overnight.

5 The reaction mixture was alkalized with 1N sodium hydroxide and the organic layer was removed. The aqueous layer was extracted with methylene chloride (3 x 150 ml). The organic layers were combined, washed with a saturated sodium chloride solution, dried over potassium carbonate, filtered, and the solvents were removed in vacuo.

10 The reaction product was further purified by chromatography using a hexanes/ethyl acetate (3:1) solution as eluent. The title product was recrystallized from hexanes and ethyl acetate as a white solid, yielding 1.55 grams (66%). MS 237, mp 53-55°C.
Analysis for C₁₆H₁₆N₂:

15 Theory: C, 81.32; H, 6.82; N, 11.85.
 Found: C, 81.06; H, 6.69; N, 12.02.

Example 33

20 **Synthesis of 1-phenyl-2-(thien-2-yl)benzimidazole**
 A solution of N-phenyl-o-phenylenediamine (1.84 g, 10 mmol) in diethyl ether (90 ml) was stirred at room temperature under a nitrogen atmosphere as an equimolar amount of 2-chlorocarbonylthiophene in diethyl ether (35 ml) was added dropwise.

25 The reaction mixture was stirred overnight at room temperature.
 The reaction mixture was alkalized with 1N sodium hydroxide and the organic layer was removed. The aqueous fraction was extracted with ethyl acetate (3 x 100 ml). The organic fractions were combined, washed with a saturated sodium chloride solution, dried over potassium carbonate, filtered, and the solvents were removed in vacuo to yield a red/brown oil.

30 The reaction product was further purified by trituration in diethyl ether. Recrystallization from ethyl acetate yielded a white solid which was homogeneous on thin layer chromatography. mp 150-152°C.

35 The intermediate prepared above in chloroform was stirred at room temperature as an equimolar amount of phosphorous

oxychloride in chloroform was added dropwise. The reaction mixture was refluxed overnight.

5 The reaction mixture was alkalinized with 1N sodium hydroxide and the organic layer was removed. The aqueous layer was extracted with methylene chloride (3 x 150 ml). The organic layers were combined, washed with a saturated sodium chloride solution, dried over potassium carbonate, filtered, and the solvents were removed in vacuo.

10 The reaction product was further purified by chromatography using a hexanes/ethyl acetate (3:1) solution as eluent. The title product was recrystallized from hexanes and ethyl acetate as clear crystals. The solvent was removed in vacuo, yielding 1.70 grams (64%). MS 277, mp 118-120°C.

Analysis for C₁₇H₁₂N₂S:

15 Theory: C, 73.62; H, 4.72; N, 10.10.
Found: C, 73.84; H, 4.48; N, 10.30.

Example 34

Synthesis of 1-phenyl-2-(3-hydroxyphenyl)benzimidazole

20 A solution of 1-phenyl-2-(3-methoxyphenyl)benzimidazole (0.20 g, 0.67 mmol) and hydrobromic acid (4 ml) and acetic acid (4 ml) was refluxed for 48 hours. The reaction mixture was cooled and extracted with diethyl ether (5 x 150 ml) at pH 3-5. The organic fractions were discarded. The aqueous phase was alkalinized to pH 8-9 and 25 extracted with ethyl acetate (5 x 150 ml). The organic layers were combined, washed with a saturated sodium chloride solution, dried over magnesium sulfate, filtered, and the solvents were removed in vacuo to yield a white solid. The solid was triturated with an ethyl acetate/diethyl ether mixture.

30 The reaction product was further purified by chromatography to yield 0.17 grams (88.6%) of a white solid. MS 287(M⁺), mp 245-247°C.

Analysis for C₁₉H₁₄N₂O • 2 H₂O:

35 Theory: C, 78.71; H, 5.01; N, 9.66.
Found: C, 78.79; H, 5.16; N, 9.70.

Example 35**Synthesis of 1-phenyl-2-pentylbenzimidazole hydrochloride**

5 A solution of N-phenyl-o-phenylenediamine (1.84 g, 10 mmol) in diethyl ether (90 ml) was stirred at room temperature as an equimolar amount of hexanoyl chloride in diethyl ether (35 ml) was added dropwise. The reaction mixture was stirred overnight at room temperature.

10 The reaction mixture was alkalinized with 1N sodium hydroxide and the organic layer was removed. The aqueous fraction was extracted with ethyl acetate (3 x 100 ml). The organic fractions were combined, washed with a saturated sodium chloride solution, dried over potassium carbonate, filtered, and the solvents were removed in vacuo to yield a red/brown oil.

15 The reaction product was further purified by trituration in diethyl ether. Recrystallization from ethyl acetate yielded a white solid which was homogeneous on thin layer chromatography.

20 The intermediate prepared above in chloroform was stirred at room temperature as an equimolar amount of phosphorous oxychloride in chloroform was added dropwise. The reaction mixture was refluxed overnight.

25 The reaction mixture was alkalinized with 1N sodium hydroxide and the organic layer was removed. The aqueous layer was extracted with methylene chloride (3 x 150 ml). The organic layers were combined, washed with a saturated sodium chloride solution, dried over potassium carbonate, filtered, and the solvents were removed in vacuo to yield a red/brown oil.

30 The reaction product was further purified by chromatography using a hexanes/ethyl acetate (3:1) solution as eluent to yield 1.82 grams (69.2%) as a red oil. The red oil was stirred in a 2N hydrochloric acid/ethanol (1:1) solution for ten minutes. The ethanol was removed in vacuo to yield 2.1 grams of a brown/green solid. The title product was recrystallized from an ethyl acetate/ethanol (1:1) solution. The solvent was removed in vacuo, yielding 1.56 grams (51.9%) of the title product as a white solid. MS 265(M⁺), mp 202-205°C.

35 Analysis for C₁₈H₂₀N₂ • HCl:

Theory: C, 71.87; H, 7.04; N, 9.31.

Found: C, 72.02; H, 7.23; N, 9.05.

Example 36

5

Synthesis of 1-phenyl-2-(2-trifluoromethylphenyl)-benzimidazole

A solution of N-phenyl-o-phenylenediamine (1.84 g, 10 mmol) in diethyl ether (90 ml) was stirred at room temperature as an equimolar amount of 2-trifluoromethylbenzoyl chloride in diethyl ether (35 ml) was added dropwise. The reaction mixture was stirred overnight at room temperature.

10

The reaction mixture was alkalinized with 1N sodium hydroxide and the organic layer was removed. The aqueous fraction was extracted with ethyl acetate (3 x 100 ml). The organic fractions were 15 combined, washed with a saturated sodium chloride solution, dried over potassium carbonate, filtered, and the solvents were removed in vacuo to yield a red/brown oil.

20

The reaction product was further purified by trituration in diethyl ether to yield a white solid which was homogeneous on thin layer chromatography. mp 161-162°C.

The intermediate prepared above in chloroform was stirred at room temperature as an equimolar amount of phosphorous oxychloride in chloroform was added dropwise. The reaction mixture was refluxed overnight.

25

The reaction mixture was alkalinized with 1N sodium hydroxide and the organic layer was removed. The aqueous layer was extracted with methylene chloride (3 x 150 ml). The organic layers were combined, washed with a saturated sodium chloride solution, dried over potassium carbonate, filtered, and the solvents were removed in vacuo to yield a red/brown mixture of oil and solid.

30

35

The reaction product was further purified by chromatography using a hexanes/ethyl acetate (3:1) solution as eluent followed by trituration in diethyl ether to yield 1.07 grams (37.2%). Recrystallization from hexanes yielded white crystals, homogeneous on thin layer chromatography. MS 338, mp 142-144°C. Analysis for $C_{20}H_{13}F_3N_2$:

Theory: C, 71.00; H, 3.87; N, 8.28.

Found: C, 70.70; H, 3.97; N, 8.12.

Example 37

5

Synthesis of 1-benzyl-2-(3,4,5-trimethoxyphenyl)-benzimidazole

A solution of o-phenylenediamine dihydrochloride (3.62 g, 20 mmol), 3,4,5-trimethoxybenzaldehyde (3.92 g, 20 mmol) and 10 triethylamine (2.02 g, 20 moles) in nitrobenzene (100 mls) was heated at 150°C for 32 hours. The majority of the nitrobenzene was distilled off by vacuum distillation (60°C pot temperature, 0.1 mm Hg). The crude product was partitioned between 1N sodium hydroxide and ethyl acetate. The ethyl acetate fraction was removed and the aqueous phase was 15 extracted with ethyl acetate (3 x 100 ml).

The organic fractions were combined, washed with brine, dried over sodium sulfate, filtered, and the solvents were removed in vacuo to yield a red brown oil which was purified by column chromatography using a hexanes/ethyl acetate (1:1) solution as the 20 eluting solvent to yield the intermediate 2-(3,4,5-trimethoxyphenyl)benzimidazole. NMR

The intermediate prepared above (0.91 g, 3.2 mmol) and 25 sodium hydride (0.26 g, 6.4 mmol) in N,N-dimethylformamide (25 ml) were stirred at room temperature as benzyl bromide (0.60 g, 6.4 mmol) was added dropwise. The resulting mixture was stirred at room temperature for 30 minutes and then heated to 120°C where it was maintained for seven days. Additional sodium hydride and benzylbromide were added as needed force the reaction forward.

The crude product was partitioned between water and ethyl 30 acetate, followed by an acid/base workup in a separatory funnel. The organic layers were washed with brine, dried over potassium carbonate, filtered, and the solvents were removed in vacuo. MS 375(M⁺) Analysis for C₂₃H₂₂N₂O₃:

Theory: C, 73.78; H, 5.92; N, 7.48.

35 Found: C, 73.99; H, 5.95; N, 7.19.

Examples 38 and 39

Synthesis of 1-phenylmethyl-2-(3,4,5-trimethoxyphenyl)-5-methoxybenzimidazole (**Example 38**) and 1-phenylmethyl-2-(3,4,5-trimethoxyphenyl)-6-methoxybenzimidazole (**Example 39**)

5 This synthesis was performed essentially as described in Example 37 except for the substitution of 4-methoxy-o-phenylenediamine in place of the o-phenylenediamine employed there. This resulted in a mixture of the regioisomers of the title products which could be
10 separated using common techniques.

Example 38: MS 404, Analysis for C₂₄H₂₄N₂O₄:

Theory: C, 71.27; H, 5.98; N, 6.92.

Found: C, 71.07; H, 6.16; N, 6.89.

Example 39: MS 404, Analysis for C₂₄H₂₄N₂O₄:

15 Theory: C, 71.27; H, 5.98; N, 6.93.

Found: C, 71.24; H, 6.11; N, 6.97.

Example 40

Synthesis of 1-(3-chlorobenzyl)-2-(3,4,5-trimethoxyphenyl)-benzimidazole

20 An amount of 2-(3,4,5-trimethoxyphenyl)-benzimidazole (1.05 g, 3.69 mmol), prepared as described in Example 37, *supra*, was added to a three-neck flask with a stir bar. The contents of the flask were placed under nitrogen atmosphere and 50 ml of N,N-dimethylformamide was added by syringe. This mixture was then
25 allowed to stir. Sodium hydride (60%, 0.41 g, 4.10 mmol) was then added to the reaction mixture and the resulting mixture was stirred for about 30 minutes.

30 The resulting grayish mixture was then placed into an oil bath and 3-chlorobenzyl bromide (0.60 ml, 4.10 mmol) was added. The temperature of the solution was then raised to 60°C and the solution was allowed to stir overnight.

35 The solution was then removed from the oil bath and allowed to cool to room temperature. Ethyl acetate (150 ml) was then added to the reaction mixture. This organic solution was extracted with

water (3 x 150 ml), followed by 25 ml of diethyl ether. The organic phase was then washed with a saturated sodium chloride solution.

The organic solution was reduced in vacuo to yield a yellow oil. To this oil ethanol (50 ml) and hexanes (20 ml) were added. The 5 yellow solution was cooled and allowed to crystallize. The crystals were recovered by filtration and then washed with 20 ml of hexanes. The liquors were reduced in vacuo and allowed to crystallize to yield a total of 1.05 grams of the title product. MS 409, 411, mp 83°C.

Analysis for $C_{23}H_{21}ClN_2O_3$:

10 Theory: C, 67.56; H, 5.18; N, 6.85.
 Found: C, 67.82; H, 5.21; N, 6.64.

Example 41

15 **Synthesis of 1-(2-chlorobenzyl)-2-(3,4,5-trimethoxyphenyl)-benzimidazole**

The title product was prepared essentially as described in Example 40, *supra*, except that 2-chlorobenzyl bromide (0.50 ml, 4.19 mmol) was employed instead of the 3-chlorobenzyl bromide, to yield 1.13 g (80%). MS 409, 411, mp 173.5°C.

20 Analysis for $C_{23}H_{21}ClN_2O_3$:

 Theory: C, 67.56; H, 5.18; N, 6.85.
 Found: C, 67.33; H, 5.21; N, 6.60.

Example 42

25 **Synthesis of 1-(4-chlorobenzyl)-2-(3,4,5-trimethoxyphenyl)-benzimidazole**

The title compound was prepared essentially as described in Example 40, *supra*, except that 4-chlorobenzyl bromide (0.75 g, 4.03 mmol) was employed instead of the 3-chlorobenzyl bromide. MS 409, 411, 30 mp 169°C.

Analysis for $C_{23}H_{21}ClN_2O_3$:

 Theory: C, 67.56; H, 5.18; N, 6.85.
 Found: C, 68.07; H, 5.34; N, 6.46.

Synthesis of 1-(2-methylbenzyl)-2-(3,4,5-trimethoxyphenyl)-benzimidazole

5 The title compound was prepared essentially as described in Example 40, *supra*, except that α -bromo-*o*-xylene (0.55 g, 4.10 mmol) was employed instead of the 3-chlorobenzyl bromide. MS 389, mp 140.5°C.

Analysis for $C_{24}H_{24}N_2O_3$:

Theory: C, 74.21; H, 6.23; N, 7.21.
10 Found: C, 73.92; H, 6.25; N, 7.05.

Example 44

Synthesis of 1-(3-methylbenzyl)-2-(3,4,5-trimethoxyphenyl)-benzimidazole

15 The title compound was prepared essentially as described in Example 40, *supra*, except that α -bromo-*m*-xylene (0.55 g, 4.10 mmol) was employed instead of the 3-chlorobenzyl bromide. MS 389, mp 78°C.
Analysis for $C_{24}H_{24}N_2O_3$:

20 Theory: C, 74.21; H, 6.23; N, 7.21.
Found: C, 73.96; H, 6.34; N, 7.01.

Example 45

Synthesis of 1-(3-methoxybenzyl)-2-(3,4,5-trimethoxyphenyl)-benzimidazole

25 The title compound was prepared essentially as described in Example 40, *supra*, except that 3-methoxybenzyl chloride (0.60 ml, 4.13 mmol) was employed instead of the 3-chlorobenzyl bromide. MS 405, mp 127°C.
30 Analysis for $C_{24}H_{24}N_2O_4$:

Theory: C, 71.27; H, 5.98; N, 6.93.
Found: C, 71.21; H, 6.04; N, 6.98.

Synthesis of 1-(4-methoxybenzyl)-2-(3,4,5-trimethoxyphenyl)-benzimidazole

5 The title compound was prepared essentially as described in Example 40, *supra*, except that 4-methoxybenzyl chloride (0.60 ml, 4.13 mmol) was employed instead of the 3-chlorobenzyl bromide. MS 405, mp 110.5°C.

Analysis for $C_{24}H_{24}N_2O_4$:

Theory: C, 71.27; H, 5.98; N, 6.93.

10 Found: C, 71.01; H, 6.01; N, 7.08.

Example 47

Synthesis of 1-(2-methoxybenzyl)-2-(3,4,5-trimethoxyphenyl)-benzimidazole

15 The title compound was prepared essentially as described in Example 40, *supra*, except that 2-methoxybenzyl chloride (50% 1.26 ml, 4.13 mmol) was employed instead of the 3-chlorobenzyl bromide. This reaction was performed at room temperature and allowed to stir for

20 about six hours. MS 405, mp 136°C.

Analysis for $C_{24}H_{24}N_2O_4$:

Theory: C, 71.27; H, 5.98; N, 6.93.

Found: C, 71.47; H, 6.13; N, 6.92.

25 Example 48

Synthesis of 1-(2-fluorobenzyl)-2-(3,4,5-trimethoxyphenyl)-benzimidazole

30 The title compound was prepared essentially as described in Example 40, *supra*, except that 2-fluorobenzyl bromide (0.48 ml, 4.33 mmol) was employed instead of the 3-chlorobenzyl bromide. MS 392, mp 153.5°C.

Analysis for $C_{23}H_{21}FN_2O_3$:

Theory: C, 70.40; H, 5.39; N, 7.14.

Found: C, 70.15; H, 5.37; N, 7.14.

Synthesis of 1-(2-trifluoromethylbenzyl)-2-(3,4,5-trimethoxyphenyl)-benzimidazole

5 The title compound was prepared essentially as described in Example 40, *supra*, except that 2-trifluoromethylbenzyl bromide (0.48 ml, 4.33 mmol) was employed instead of the 3-chlorobenzyl bromide. MS 442, mp 144°C.

Analysis for $C_{24}H_{21}F_3N_2O_3$:

Theory: C, 65.15; H, 4.78; N, 6.33.
10 Found: C, 65.18; H, 4.75; N, 6.28.

Example 50

Synthesis of 1-(2-iodobenzyl)-2-(3,4,5-trimethoxyphenyl)-benzimidazole

15 The title compound was prepared essentially as described in Example 40, *supra*, except that 2-iodobenzyl bromide (1.0 ml, 4.33 mmol) was employed instead of the 3-chlorobenzyl bromide. MS 500, mp 179°C.

Analysis for $C_{23}H_{21}IN_2O_3$:

20 Theory: C, 55.21; H, 4.23; N, 5.60.
 Found: C, 55.26; H, 4.27; N, 5.71.

Example 51

Synthesis of 1-(2-bromobenzyl)-2-(3,4,5-trimethoxyphenyl)-benzimidazole

25 The title compound was prepared essentially as described in Example 40, *supra*, except that 2-bromobenzyl bromide (1.0 ml, 4.33 mmol) was employed instead of the 3-chlorobenzyl bromide. MS 452, 454, mp 152°C.

30 Analysis for $C_{23}H_{21}BrN_2O_3$:

 Theory: C, 60.94; H, 4.67; N, 6.18.
 Found: C, 61.18; H, 4.62; N, 6.09.

Example 52

35 **Synthesis of 1-(2,6-dichlorobenzyl)-2-(3,4,5-trimethoxyphenyl)-benzimidazole**

The title compound was prepared essentially as described in Example 40, *supra*, except that 2,6-dichlorobenzyl bromide (0.81 g, 4.10 mmol) was employed instead of the 3-chlorobenzyl bromide. mp 5 157°C. MS 443, 445, NMR, IR.
Analysis for $C_{23}H_{20}Cl_2N_2O_3$:

Theory: C, 62.31; H, 4.55; N, 6.32.
Found: C, 62.84; H, 4.57; N, 6.31.

Example 53

Synthesis of 1-(3,4-dichlorobenzyl)-2-(3,4,5-trimethoxyphenyl)-benzimidazole

The title compound was prepared essentially as described in Example 40, *supra*, except that 3,4-dichlorobenzyl bromide (0.90 g, 4.45 mmol) was employed instead of the 3-chlorobenzyl bromide. mp 145°C, MS 443, 445, NMR, IR.

Theory: C, 62.31; H, 4.55; N, 6.32.
 Found: C, 62.35; H, 4.65; N, 6.17

Example 54

Synthesis of 1-(2,4-dichlorobenzyl)-2-(3,4,5-trimethoxyphenyl)-benzimidazole

25 The title compound was prepared essentially as described in Example 40, *supra*, except that 2,4-dichlorobenzyl bromide (0.45 g, 2.23 mmol) was employed instead of the 3-chlorobenzyl bromide. mp 186°C. MS 442, 445. NMR, IR.

30 Analysis for $\text{Ca}_2\text{HgCl}_2\text{NaO}_2$:

Theory: C, 62.31; H, 4.55; N, 6.32.
Found: C, 62.22; H, 4.65; N, 6.34

Example 55

35 Synthesis of 1-(4-methylbenzyl)-2-(3,4,5-trimethoxyphenyl)-benzimidazole

The title compound was prepared essentially as described in Example 40, *supra*, except that 4-methylbenzyl bromide (0.45 g, 2.23 mmol) was employed instead of the 3-chlorobenzyl bromide. MS 389, mp 5 84.5°C.

Analysis for $C_{24}H_{24}N_2O_3$:

Theory: C, 74.21; H, 6.23; N, 7.21.

Found: C, 73.91; H, 6.23; N, 6.98.

10

Example 56

Synthesis of 1-(2-chlorobenzyl)-2-(3-methylphenyl)-benzimidazole

The intermediate 2-(3-methylphenyl)-benzimidazole was prepared by first mixing reacting 1-amino-2-nitrobenzene (8.50 g, 61.54 15 mmol) with toluene (180 ml) and heating to 100°C. To this mixture was then added 20 ml of N,N-diethylaniline and the reaction vessel was placed under a nitrogen atmosphere. To this solution was then added 3-methylbenzoyl chloride (24 ml, 132 mmol) and this mixture was then stirred overnight.

20 After stirring, the reaction mixture was neutralized by the addition of 300 ml of 1N hydrochloric acid and 300 ml of ethyl acetate. This was then stirred for about 30 minutes. The organic phase was then removed and washed with water, followed by drying over magnesium sulfate and reduction in *vacuo*, yielding yellow crystals of the 25 intermediate 1-[(3-methylphenyl)carbonylamino]-2-nitrobenzene. The nitro group of the above intermediate was then reduced by catalytic hydrogenation employing a palladium on activated carbon catalyst resulting in the substituted 1,2-phenylenediamine.

30 The substituted 1,2-phenylenediamine (1.01 g, 4.46 mmol) was then cyclized using phosphorous oxychloride (1.01 g, 6.6 mmol) as described *supra* to produce 2-(3-methylphenyl)benzimidazole.

The title compound was then produced by reacting the 2-(3-methylphenyl)benzimidazole (0.75 g, 3.60 mmol) with 2-chlorobenzyl chloride (0.50 ml, 4.19 mmol) essentially as described in Example 40, 35 *supra*. MS 332, 334, mp 117°C.

Analysis for $C_{21}H_{17}ClN_2$:

- 57 -

Theory: C, 75.78; H, 5.15; N, 8.42.
Found: C, 75.99; H, 5.24; N, 8.43.

5 The following compounds were synthesized essentially as described in Example 56 by reacting 2-(3-methylphenyl)benzimidazole with the appropriately substituted benzyl halide.

Example 57

10 1-(3-Chlorobenzyl)-2-(3-methylphenyl)benzimidazole.
MS 332, 334, mp 90°C.
Analysis for $C_{21}H_{17}ClN_2$:

Theory: C, 75.78; H, 5.15; N, 8.42.
Found: C, 75.51; H, 5.20; N, 8.56.

15 Example 58

1-(4-Chlorobenzyl)-2-(3-methylphenyl)benzimidazole.
MS 332, 334, mp 108.5°C.
Analysis for $C_{21}H_{17}ClN_2$:

Theory: C, 75.78; H, 5.15; N, 8.42.
20 Found: C, 75.55; H, 5.29; N, 8.37.

Example 60

1-(2-Bromobenzyl)-2-(3-methylphenyl)benzimidazole.
MS 376, 378, mp 134°C.
25 Analysis for $C_{21}H_{17}BrN_2$:

Theory: C, 66.85; H, 4.54; N, 7.42.
Found: C, 67.13; H, 4.60; N, 7.34.

Example 61

30 1-(2-Iodobenzyl)-2-(3-methylphenyl)benzimidazole.
MS 424, 425, mp 129°C.
Analysis for $C_{21}H_{17}IN_2 \cdot 0.1$ hexanes:

Theory: C, 59.93; H, 4.28; N, 6.47.
Found: C, 60.20; H, 4.12; N, 6.87.

35

Example 62

- 58 -

1-(2,6-Dichlorobenzyl)-2-(3-methylphenyl)benzimidazole.

mp 148°C, NMR, IR, MS 366, 368.

Analysis for C₂₁H₁₆Cl₂N₂ • 0.1 hexanes:

Theory: C, 69.02; H, 4.67; N, 7.45.

5 Found: C, 69.25; H, 4.42; N, 7.21.

Example 63

1-(2,4-Dichlorobenzyl)-2-(3-methylphenyl)benzimidazole.

mp 161°C, MS 366, 368, IR, NMR.

10 Analysis for C₂₁H₁₆Cl₂N₂:

Theory: C, 68.68; H, 4.39; N, 7.63.

Found: C, 68.48; H, 4.61; N, 7.70.

Example 64

15 1-(3,4-Dichlorobenzyl)-2-(3-methylphenyl)benzimidazole.

mp 85.5°C, MS 366, 368, IR, NMR.

Analysis for C₂₁H₁₆Cl₂N₂:

Theory: C, 68.68; H, 4.39; N, 7.63.

Found: C, 68.88; H, 4.41; N, 7.50.

20

Example 65

1-(3-Methoxybenzyl)-2-(3-methylphenyl)benzimidazole.

Oil at room temperature. NMR, IR, MS 328.

Analysis for C₂₂H₂₀N₂O:

25 Theory: C, 80.46; H, 6.14; N, 8.53.

Found: C, 81.39; H, 6.70; N, 8.23.

Example 66

1-(4-Methoxybenzyl)-2-(3-methylphenyl)benzimidazole.

30 mp 91°C, NMR, IR, MS 328.

Analysis for C₂₂H₂₀N₂O:

Theory: C, 80.46; H, 6.14; N, 8.53.

Found: C, 80.68; H, 6.31; N, 8.63.

35

Example 67

Synthesis of 1-(3-hydroxybenzyl)-2-(3-methylphenyl)benzimidazole hydrobromide.

This compound was prepared by first synthesizing 1-(3-methoxybenzyl)-2-(3-methylphenyl)benzimidazole as described in Example 65, *supra*. With an amount of the compound of Example 65 (4.31 g, 13.12 mmol) in glacial acetic acid (50 ml) and hydrobromic acid (300 ml of a 48% w/v in acetic acid solution). This mixture was stirred for 2 hours while warming to reflux. The mixture was then stirred at 10 reflux for about three hours.

The reaction mixture was then allowed to cool to room temperature after which time the reaction mixture was partitioned between water (1 liter) and methylene chloride, followed by extraction with methylene chloride (3 x 500 ml). The organic fractions were 15 combined and dried over magnesium sulfate. After reducing the volume of the organic solvents in vacuo, the organic fraction was washed with water (3 x 250 ml) to remove residual hydrobromic acid. The organic phases were combined and dried in vacuo to yield a gray solid which was washed with diethyl ether (2 x 250 ml) and dried in a 20 vacuum oven. NMR, IR, MS 314, mp 235°C.

Analysis for $C_{21}H_{18}N_2O \cdot HBr$:

Theory: C, 63.81; H, 4.84; N, 7.09.

Found: C, 64.45; H, 5.02; N, 7.23.

25

Example 69

Synthesis of 1-benzyl-2-(3,4,5-trimethoxyphenyl)-6-(hydroxy)-benzimidazole hydrochloride.

The title compound was prepared by first reacting 4-amino-30 3-nitrophenol (25.0 g, 162.2 mmol) with 3,4,5-trimethoxybenzoyl chloride (112 g, 485.6 mmol) in N,N-diethylaniline (69 ml) and toluene (500 ml). The reaction mixture was stirred and the temperature was raised to 100°C. The solution was maintained at this temperature for about 6 hours as a yellow precipitate formed. The reaction mixture was then 35 partitioned between 1N hydrochloric acid (250 ml) and ethyl acetate (250 ml). The crystals were then removed by filtration and washed with ethyl

acetate (300 ml) and water (300 ml) to yield the intermediate 1-(3,4,5-trimethoxy)benzyl ester of 4-(3,4,5-trimethoxyphenylcarbonylamino)-2-nitrophenol.

5 A benzyl group was then substituted on the nitro group by reacting the above intermediate (10 g, 18.4 mmol) with benzaldehyde (6 ml) in N,N-dimethylformamide (100 ml) under a hydrogen atmosphere (60°C at 60 p.s.i.) with 6.0 g of a palladium on activated carbon catalyst.

10 The benzimidazole ring was closed using phosphorous oxychloride in chloroform as described *supra*. The ester on the 6-hydroxy group of the benzimidazole was removed by incubating the intermediate in 1N sodium hydroxide (500 ml) and tetrahydrofuran (500 ml). This solution was stirred overnight, followed by acidification with a sufficient amount of 1 N hydrochloric acid to reduce the pH to 1.0. This solution was then washed with ethyl acetate (2 x 500 ml). The organic 15 fractions were combined, dried over magnesium sulfate, and the solvents removed *in vacuo* to yield a brownish/red solid. The title compound was further purified by flash chromatography to yield a grayish solid. MS 390.

Analysis for C₂₃H₂₂N₂O₄ • HCl:

20 Theory: C, 64.71; H, 5.43; N, 6.56.
Found: C, 65.12; H, 5.40; N, 6.63.

Example 70

Synthesis of 1-benzyl-2-(3,4,5-trimethoxyphenyl)-6-[2-(4-25 morpholinyl)ethoxy]benzimidazole.

The title compound was prepared by reacting the compound of Example 69, *supra*, (0.23 g, 0.59 mmol) with 4-(2-chloroethyl)morpholine hydrochloride (1.10 g, 5.91 mmol) and 30 potassium carbonate (1.63 g, 11.80 mmol) in acetone. The reaction conditions employed were essentially as described for previous alkylations. MS 503.

Analysis for C₂₉H₃₃N₃O₅:

35 Theory: C, 69.17; H, 6.60; N, 8.34.
Found: C, 69.10; H, 6.70; N, 8.42.

- 61 -

Example 71

Synthesis of 1-benzyl-2-(3,4,5-trimethoxyphenyl)-6-[2-(1-piperidinyl)ethoxy]benzimidazole.

5 The title compound was prepared essentially as described in Example 70 except that 1-(2-chloroethyl)piperidine hydrochloride was employed in place of 4-(2-chloroethyl)morpholine hydrochloride. MS 501. Analysis for $C_{30}H_{35}N_3O_4$:

Theory: C, 71.83; H, 7.03; N, 8.38.

10 Found: C, 71.95; H, 7.27; N, 8.17.

Example 72

Synthesis of 1-benzyl-2-(3,4,5-trimethoxyphenyl)-6-[2-(1-pyrrolidinyl)ethoxy]benzimidazole.

15 The title compound was prepared essentially as described in Example 70 except that 1-(2-chloroethyl)pyrrolidine hydrochloride was employed in place of 4-(2-chloroethyl)morpholine hydrochloride. MS 488. Analysis for $C_{29}H_{33}N_3O_4$:

20 Theory: C, 71.44; H, 6.82; N, 8.62.

Found: C, 71.61; H, 7.05; N, 8.87.

Example 73

Synthesis of 1-benzyl-2-(3,4,5-trimethoxyphenyl)-6-[2-(1-hexamethyleneiminyl)ethoxy]benzimidazole.

30 The title compound was prepared essentially as described in Example 70 except that 1-(2-chloroethyl)hexamethyleneimine hydrochloride was employed in place of 4-(2-chloroethyl)morpholine hydrochloride. NMR, IR, MS 515, mp 122.5°C. Analysis for $C_{31}H_{37}N_3O_4$:

Theory: C, 72.21; H, 7.23; N, 8.15.

Found: C, 72.18; H, 7.19; N, 8.42.

35

Example 74

Synthesis of 1-benzyl-2-(3,4,5-trimethoxyphenyl)-6-[3-(1-piperidinyl)propoxy]benzimidazole.

5 The title compound was prepared essentially as described in Example 70 except that 1-(3-chloropropyl)piperidine hydrochloride was employed in place of 4-(2-chloroethyl)morpholine hydrochloride. mp 92°C, NMR, IR, MS 515.

Analysis for $C_{31}H_{37}N_3O_4$:

Theory: C, 72.21; H, 7.23; N, 8.15.

10 Found: C, 72.50; H, 7.26; N, 7.90.

Example 75

Synthesis of 1-benzyl-2-(3,4,5-trimethoxyphenyl)-6-(3-chloropropoxy)benzimidazole.

15 The title compound was prepared essentially as described in Example 70 except that 1-chloro-3-iodopropane was employed in place of 4-(2-chloroethyl)morpholine hydrochloride. mp 118.5°C, MS 466, 468, NMR, IR.

20 Analysis for $C_{26}H_{27}ClN_2O_4 \cdot 0.5 H_2O$:

Theory: C, 65.61; H, 5.93; N, 5.89.

Found: C, 65.92; H, 5.74; N, 5.91.

Example 76

25 Synthesis of 1-benzyl-2-(3,4,5-trimethoxyphenyl)-6-(2-chloroethoxy)benzimidazole.

30 The title compound was prepared essentially as described in Example 70 except that 1-bromo-2-chloroethane was employed in place of 4-(2-chloroethyl)morpholine hydrochloride. IR, NMR, MS 452, 454, mp 129°C.

Analysis for $C_{25}H_{25}ClN_2O_4$:

Theory: C, 66.30; H, 5.56; N, 6.19.

Found: C, 67.33; H, 5.41; N, 6.61.

35

Example 77

Synthesis of 1-benzyl-2-(3,4,5-trimethoxyphenyl)-6-[2-[4-(piperidin-1-yl)piperidin-1-yl]ethoxy]benzimidazole.

The title compound was prepared by reacting the compound 5 of Example 76, *supra*, (0.45 g, 1.0 mmol) with 4-(piperidin-1-yl)piperidine (2.0 g, 11.9 mmol) in the presence of the base N,N-diisopropylethylamine, tetra-n-butylammonium iodide and acetonitrile at 80°C. After incubating overnight at 80°C the reaction was washed with water (2 x 500 ml), followed by a wash with a saturated sodium 10 chloride solution (1 x 500 ml). The organic phase was then dried over potassium carbonate and the solvents were removed in vacuo to yield a light brown oil. The desired product was purified by chromatography and triturated with diethyl ether to yield a light brown powder, which was removed by filtration and washed with diethyl ether to yield the 15 purified title compound. MS 584, 585, NMR, IR, mp 143°C.

Analysis for C₃₅H₄₄N₄O₄:

Theory: C, 71.89; H, 7.58; N, 9.58.

Found: C, 72.11; H, 7.62; N, 9.67.

20

Example 78

Synthesis of 1-benzyl-2-(3,4,5-trimethoxyphenyl)-6-[1-methyl-2-(N,N-dimethylamino)ethoxy]benzimidazole.

The title compound was prepared by reacting the compound 25 of Example 70, *supra*, 0.45 g, 1.15 mmol) with 1-methyl-2-dimethylaminoethyl chloride (1.82 g, 11.51 mmol) and potassium chloride (3.18 g, 23.01 mmol) in 100 ml of acetone. The reactants were admixed and then heated to reflux overnight.

After the overnight incubation the reaction mixture was 30 acidified by adding 500 ml of 1N hydrochloric acid and then washed with ethyl acetate (2 x 250 ml). The aqueous layer was then basified and extracted with ethyl acetate (500 ml). The organic fractions were combined and washed with a saturated sodium chloride solution and dried over potassium carbonate. The solvents were removed in vacuo to 35 yield a yellow oil which was triturated with hexanes, forming a white solid. This was further purified by crystallizing from 10:1

hexanes:ethanol to yield the desired title product. IR, NMR, MS 475, 476, mp 93°C.

Analysis for C₂₈H₃₃N₃O₄:

Theory: C, 70.71; H, 6.99; N, 8.84.

5 Found: C, 70.93; H, 7.01; N, 8.92.

Example 79

Synthesis of 1-benzyl-2-(3,4,5-trimethoxyphenyl)-6-[2-(N,N-dimethylamino)ethoxy]benzimidazole.

10

The title compound was prepared essentially as described in Example 78, *supra*, except that 2-dimethylaminoethyl chloride was employed in place of the 1-methyl-2-dimethylaminoethyl chloride. IR, NMR, MS 461, mp 108°C.

15

Analysis for C₂₇H₃₁N₃O₄ • 0.1 hexanes:

Theory: C, 70.51; H, 6.95; N, 8.94.

Found: C, 70.98; H, 6.60; N, 8.62.

Example 80

20

Synthesis of 1-benzyl-2-(3,4,5-trimethoxyphenyl)-6-[3-(N,N-dimethylamino)propoxy]benzimidazole.

25

The title compound was prepared essentially as described in Example 78, *supra*, except that 3-dimethylaminopropyl chloride was employed in place of the 1-methyl-2-dimethylaminoethyl chloride. IR, NMR, MS 475, mp 112°C.

Analysis for C₂₈H₃₃N₃O₄:

Theory: C, 70.71; H, 6.99; N, 8.83.

Found: C, 70.42; H, 6.97; N, 8.68.

30

Example 81

Synthesis of 1-benzyl-2-(3,4,5-trimethoxyphenyl)-6-[2-(N,N-diisopropylamino)ethoxy]benzimidazole.

35

The title compound was prepared essentially as described in Example 78, *supra*, except that 2-diisopropylaminoethyl chloride was

- 65 -

employed in place of the 1-methyl-2-dimethylaminoethyl chloride. IR, NMR, MS 517, 518, mp 101°C.

Analysis for C₃₁H₃₉N₃O₄:

Theory: C, 71.93; H, 7.59; N, 8.12.

5 Found: C, 71.91; H, 7.76; N, 7.98.

Example 83

Synthesis of 1-benzyl-2-(3,4,5-trimethoxyphenyl)-6-[2-(4-methyl-1-piperazinyl)ethoxy]benzimidazole.

10

The title compound was prepared essentially as described in Example 77, *supra*, employing the compound of Example 76, except that 1-methylpiperazine was employed in place of the 4-(piperdin-1-yl)piperidine. IR, NMR, MS 517, mp 113°C.

15

Analysis for C₃₀H₃₆N₄O₄ • 0.5 H₂O:

Theory: C, 68.55; H, 7.09; N, 10.66.

Found: C, 68.83; H, 7.19; N, 10.98.

Example 84

20

Synthesis of 1-benzyl-2-(3-methylphenyl)-6-hydroxybenzimidazole

The title compound was prepared essentially as described in Example 69, *supra*, except that 3-methylbenzoyl chloride (18.8 g, 121.6 mmol) was employed instead of the 3,4,5-trimethoxybenzoyl chloride. MS 314

25 Analysis for C₂₁H₁₈N₂O:

Theory: C, 80.23; H, 5.77; N, 8.91.

Found: C, 80.10; H, 5.85; N, 8.81.

30

Example 85

Synthesis of 1-benzyl-2-(3-methylphenyl)-6-[2-(1-piperidinyl)ethoxy]benzimidazole

35

5 The title compound was synthesized by reacting the compound of Example 84, *supra*, (0.25 g, 0.79 mmol) with 2-(piperdiny-1-yl)ethyl chloride (17.46 g, 7.9 mmol) in the presence of potassium carbonate (2.20 g, 15.9 mmol) and acetone (150 ml). These contents were added to a flask and refluxed overnight.

10 After the overnight incubation, the reaction mixture was quenched by adding 0.5 N hydrochloric acid (300 ml) and was washed with ethyl acetate (300 ml). The aqueous layer was basified with 1N sodium hydroxide until the pH=10. This aqueous layer was extracted with ethyl acetate (300 ml). The organic fractions were combined and the solvent volume was reduced in vacuo, leaving a yellow oil. Diethyl ether and hexanes were added to this oil and it was then placed at -20°C until crystals of the title product formed, which were then harvested by filtration. MS 425, 426.

15 Analysis for C₂₈H₃₁N₃O:

Theory: C, 79.03; H, 7.34; N, 9.87.

Found: C, 78.75; H, 7.47; N, 10.09.

Example 86

20 Synthesis of 1-benzyl-2-(3-methylphenyl)-6-[2-(1-pyrrolidinyl)ethoxy]benzimidazole.

25 The title product was prepared essentially as described in Example 85, *supra*, except that 1-(2-chloroethyl)pyrrolidine hydrochloride was employed instead of the 2-(piperdiny-1-yl)ethyl chloride. MS 411.

Analysis for C₂₇H₂₉N₃O:

Theory: C, 78.80; H, 7.10; N, 10.21.

30 Found: C, 78.85; H, 7.14; N, 10.08.

Example 87

35 Synthesis of 1-benzyl-2-(3-methylphenyl)-6-[2-(4-morpholinyl)ethoxy]benzimidazole

The title product was prepared essentially as described in Example 85, *supra*, except that 4-(2-chloroethyl)morpholine hydrochloride was employed instead of the 2-(piperdanyl-1-yl)ethyl chloride. MS 427.

5 Analysis for C₂₇H₂₉N₃O₂:

Theory: C, 75.85; H, 6.84; N, 9.83.

Found: C, 75.75; H, 6.89; N, 9.88.

Example 88

10

Synthesis of 1-benzyl-2-(3-methylphenyl)-6-[2-(N,N-dimethylamino)ethoxy]benzimidazole

The title product was prepared essentially as described in Example 85, *supra*, except that 2-(N,N-dimethylamino)ethyl chloride was employed instead of the 2-(piperdanyl-1-yl)ethyl chloride. MS 385.

Analysis for C₂₅H₂₇N₃O:

Theory: C, 77.89; H, 7.06; N, 10.90.

Found: C, 77.88; H, 7.14; N, 10.74.

20

Example 89

Synthesis of 1-benzyl-2-(3-methylphenyl)-6-[2-(N,N-dibenzylamino)ethoxy]benzimidazole

25

The title product was prepared essentially as described in Example 85, *supra*, except that 2-(N,N-dibenzylamino)ethyl chloride was employed instead of the 2-(piperdanyl-1-yl)ethyl chloride. MS 537.

Analysis for C₃₇H₃₅N₃O:

30 Theory: C, 82.65; H, 6.56; N, 7.82.

Found: C, 82.47; H, 6.73; N, 7.81.

Example 90

35 Synthesis of 1-benzyl-2-(3-methylphenyl)-6-[2-(N-phenyl-N-ethylamino)ethoxy]benzimidazole

5 The title product was prepared essentially as described in Example 85, *supra*, except that 2-(N-benzyl-N-ethylamino)ethyl chloride was employed instead of the 2-(piperdiny1-1-yl)ethyl chloride. MS 461, 462.

Analysis for C₃₁H₃₁N₃O:

Theory: C, 80.66; H, 6.77; N, 9.10.

Found: C, 80.37; H, 6.81; N, 8.98.

10

Example 91

Synthesis of 1-benzyl-2-(3-methylphenyl)-6-[2-(N,N-isopropylamino)ethoxy]benzimidazole

15 The title product was prepared essentially as described in Example 85, *supra*, except that 2-(N,N-diisopropylamino)ethyl chloride was employed instead of the 2-(piperdiny1-1-yl)ethyl chloride. MS 441. Analysis for C₂₉H₃₅N₃O:

Theory: C, 78.87; H, 7.99; N, 5.51.

20 Found: C, 79.07; H, 8.12; N, 5.60.

Example 92

25 Synthesis of 1-benzyl-2-(3-methylphenyl)-6-[2-(hexamethyleneimin-1-yl)ethoxy]benzimidazole

30 The title product was prepared essentially as described in Example 85, *supra*, except that 2-(hexamethyleneimin-1-yl)ethyl chloride was employed instead of the 2-(piperdiny1-1-yl)ethyl chloride. MS 439.

Analysis for C₂₉H₃₃N₃O:

Theory: C, 79.23; H, 7.57; N, 9.56.

Found: C, 79.45; H, 7.72; N, 9.66.

35

Example 93

- 69 -

Synthesis of 1-benzyl-2-(3-methylphenyl)-6-[2-(N,N-diethylamino)ethoxy]-benzimidazole

10 The title product was prepared essentially as described in
5 Example 85, *supra*, except that 2-(N,N-diethylamino)ethyl chloride was
employed instead of the 2-(piperdinyl-1-yl)ethyl chloride. MS 413, 414.
Analysis for C₂₇H₃₁N₃O • 0.25 H₂O:

Theory: C, 77.57; H, 7.59; N, 10.05.

Found: C, 77.60; H, 7.42; N, 9.74.

15

Example 94

Synthesis of 1-benzyl-2-(3-methylphenyl)-6-[3-(N,N-dimethylamino)propoxy]benzimidazole

15

The title product was prepared essentially as described in
Example 85, *supra*, except that 3-(N,N-dimethylamino)propyl chloride was
employed instead of the 2-(piperdinyl-1-yl)ethyl chloride. MS 399.
Analysis for C₂₆H₂₉N₃O:

20

Theory: C, 78.16; H, 7.32; N, 10.52.

Found: C, 77.93; H, 7.32; N, 10.25.

Example 95

25 Synthesis of 1-benzyl-2-(3-methylphenyl)-6-[3-(piperidin-1-yl)propoxy]-benzimidazole.

30 The title product was prepared essentially as described in
Example 85, *supra*, except that 3-(piperidin-1-yl)propyl chloride was
employed instead of the 2-(piperdinyl-1-yl)ethyl chloride. mp 84°C, MS
439, NMR, IR.

Analysis for C₂₉H₃₃N₃O:

Theory: C, 79.23; H, 7.57; N, 9.55.

Found: C, 79.39; H, 7.59; N, 9.59.

35

Example 96

Synthesis of 1-benzyl-2-(3-methylphenyl)-6-[2-(N,N-dimethylamino)propoxy]-benzimidazole

5 The title product was prepared essentially as described in Example 85, *supra*, except that 2-(N,N-dimethylamino)propyl chloride was employed instead of the 2-(piperdanyl-1-yl)ethyl chloride. mp 74°C, NMR, IR, MS 399, 400.

Analysis for C₂₆H₂₉N₃O:

10 Theory: C, 78.16; H, 7.32; N, 10.52.
 Found: C, 79.58; H, 7.44; N, 10.49.

Example 97

15 Synthesis of 1-benzyl-2-(3-methylphenyl)-6-(3-chloropropoxy)-benzimidazole

20 The title product was prepared essentially as described in Example 85, *supra*, except that 3-chloropropyl iodide was employed instead of the 2-(piperdanyl-1-yl)ethyl chloride. mp 97°C, NMR, IR, MS 390, 391.

Analysis for C₂₄H₂₃ClN₂O:

Theory: C, 73.74; H, 5.93; N, 7.17.
Found: C, 73.61; H, 5.94; N, 7.39.

25

Example 98

Synthesis of 1-benzyl-2-(3-methylphenyl)-6-(2-chloroethoxy)-benzimidazole

30 The title product was prepared essentially as described in Example 85, *supra*, except that 2-chloroethyl bromide was employed instead of the 2-(piperdanyl-1-yl)ethyl chloride. mp 88°C, MS 376, 378, NMR, IR.

35 Analysis for C₂₃H₂₁ClN₂O:

Theory: C, 73.30; H, 5.62; N, 7.43.

Found: C, 73.04; H, 5.67; N, 7.65.

Example 99

5 **Synthesis of 1-benzyl-2-(3-methylphenyl)-6-[3-(morpholin-4-yl)propoxy)benzimidazole.**

10 The title compound was prepared by first adding morpholine (1.02 g, 11.77 mmol) and the compound of Example 97, 15 *supra*, (0.39 g, 1.00 mmol) to 125 ml of acetonitrile while stirring under nitrogen purge. To this mixture is then added diisopropylethyl aniline (1.51 ml, 8.67 mmol) dropwise. This reaction mixture is then allowed to stir overnight.

15 After the overnight stirring, additional diisopropyl aniline (1.00 ml) is added and the mixture is then heated to 60°C and maintained at this temperature for about 3 days. The reaction mixture was then washed with water (3 x 250 ml) and the solvents were removed in vacuo, resulting in a yellow oil.

20 The yellow oil was further purified by chromatography using ethyl acetate, followed by removal of the solvents in vacuo, and trituration with hexanes to afford yellow crystals. NMR, MS 441, IR, mp 120°C.

Analysis for C₂₈H₃₁N₃O₂:

Theory: C, 76.16; H, 7.08; N, 9.52.

25 Found: C, 76.39; H, 7.26; N, 9.54.

Example 100

30 **Synthesis of 1-benzyl-2-(3-methylphenyl)-6-[3-(pyrrolidin-1-yl)propoxy)benzimidazole**

35 The title compound was prepared essentially as described in Example 99, *supra*, except that pyrrolidine was employed in place of morpholine. mp 120°C, NMR, IR, MS 425.

Analysis for C₂₈H₃₁N₃O:

Theory: C, 79.03; H, 7.34; N, 9.87.

- 72 -

Found: C, 79.22; H, 7.39; N, 9.83.

Example 101

5 **Synthesis of 1-benzyl-2-(3-methylphenyl)-6-[3-(hexamethyleneimin-1-yl)propoxy]benzimidazole**

10 The title compound was prepared essentially as described in Example 99, *supra*, except that hexamethyleneimine was employed in place of morpholine. mp 69.5°C, NMR, IR, MS 453, 454.
Analysis for C₃₀H₃₅N₃O:

Theory: C, 79.43; H, 7.78; N, 9.26.

Found: C, 79.60; H, 7.88; N, 9.28.

15

Example 102

Synthesis of 1-benzyl-2-(3-methylphenyl)-6-[3-(heptamethyleneimin-1-yl)propoxy]benzimidazole

20 The title compound was by reacting the compound of Example 97, *supra*, (0.39 g, 1.00 mmol) with heptamethyleneimine (10 g, 88.3 mmol) in the presence of N,N-diisopropylethylamine (2 ml) and acetonitrile (5 ml). This reaction mixture was raised to 80°C and allowed to stir at that temperature overnight. The compound was
25 purified essentially as described in Example 99, *supra*. NMR, MS 467, mp 77°C.

Analysis for C₃₁H₃₇N₃O:

Theory: C, 79.62; H, 7.97; N, 8.98.

Found: C, 79.50; H, 7.99; N, 8.99.

30

Example 103

Synthesis of 1-benzyl-2-(3-methylphenyl)-6-[2-(4-methyl-piperazin-1-yl)ethoxy]benzimidazole

35

The title compound was prepared by reacting the compound of Example 98, *supra*, (1.89 g, 5.01 mmol) with 1-methyl-piperazine (65 ml) in the presence of N,N-diisopropylethyl amine (4 ml) and N,N-dimethylformamide (100 ml) under nitrogen atmosphere. This reaction mixture was heated to 50°C and stirred overnight at that temperature. The compound was purified essentially as described in Example 99, *supra*. NMR, IR, MS 440, 441, mp 91°C.

5 Analysis for C₂₈H₃₂N₄O:

Theory: C, 76.33; H, 7.32; N, 12.72.
10 Found: C, 76.19; H, 7.15; N, 12.96.

Example 104

15 **Synthesis of 1-(2-trifluoromethylbenzyl)-2-(3,4,5-trimethoxyphenyl)-6-hydroxybenzimidazole**

The title compound was prepared by first reacting 3,4,5-trimethoxybenzoyl chloride (112.0 g, 485.6 mmol) with 4-amino-3-nitrophenol (25.0 g, 162.2 mmol) in N,N-diethylaniline (69 ml) and toluene (500 ml). This reaction mixture was heated to 100°C and maintained at that temperature for about 6 hours. The intermediate ester of 4-(3,4,5-trimethoxyphenylcarbonylamino)-3-nitrophenol was purified essentially as described in Example 69, *supra*.

20 The nitro moiety of the above-described intermediate was reduced to an amino group by catalytic hydrogenation using a palladium on activated carbon catalyst as described previously. This primary amino group was then alkylated by reacting with 2-trifluoromethylbenzyl bromide in the presence of N,N-diisopropylethyl amine and tetrahydrofuran. This mixture was allowed to reflux 25 overnight.

30 The reaction mixture was then washed with water (5 x 500 ml) followed by a wash with saturated sodium chloride (500 ml). The organic phase was dried over potassium carbonate, and the solvents were removed in vacuo, leaving a brown solid. Following trituration in 35 diethyl ether a gray solid formed.

5 The benzimidazole ring was closed using phosphorous oxychloride in chloroform as previously described. The protecting ester on the 6-hydroxy of the benzimidazole ring was removed by incubating the protected compound in 1N sodium hydroxide in tetrahydrofuran to cleave this group, leaving the title compound. NMR, IR, MS 458, mp 191°C.

Analysis for $C_{24}H_{21}F_3N_2O_4$:

Theory: C, 62.88; H, 4.62; N, 6.11.

Found: C, 62.89; H, 4.88; N, 5.90.

10

Example 105

Synthesis of 1-(2-trifluoromethylbenzyl)-2-(3,4,5-trimethoxyphenyl)-6-[2-(piperidin-1-yl)ethoxy]benzimidazole

15

The title compound was prepared by reacting the compound of Example 104 with 1-(2-chloroethyl)piperidine hydrochloride essentially as previously described. mp 167°C, NMR, IR, MS 570.

Analysis for $C_{31}H_{34}F_3N_3O_4$:

20

Theory: C, 65.37; H, 6.02; N, 7.38.

Found: C, 65.40; H, 6.02; N, 7.41.

Example 106

25

Synthesis of 1-(2-trifluoromethylbenzyl)-2-(3,4,5-trimethoxyphenyl)-6-[2-(N,N-dimethylamino)propoxy]benzimidazole

30

The title compound was prepared by reacting the compound of Example 104 with 2-(N,N-dimethylamino)propyl chloride essentially as previously described. mp 163°C, NMR, IR, MS 543, 544.

Analysis for $C_{29}H_{32}F_3N_3O_4$:

Theory: C, 64.08; H, 5.93; N, 7.73.

Found: C, 64.00; H, 5.86; N, 7.68.

35

Example 107

Synthesis of 1-(2-trifluoromethylbenzyl)-2-(3,4,5-trimethoxyphenyl)-6-[2-(N,N-dimethylamino)ethoxy]-benzimidazole

5 The title compound was prepared by reacting the compound of Example 104 with 2-(N,N-dimethylamino)ethyl chloride essentially as previously described. mp 151°C, NMR, IR, MS 529.
Analysis for $C_{28}H_{30}F_3N_3O_4$:

Theory: C, 63.51; H, 5.71; N, 7.94.

Found: C, 63.79; H, 5.57; N, 8.02.

10

Example 108

15 **Synthesis of 1-(2-trifluoromethylbenzyl)-2-(3,4,5-trimethoxyphenyl)-6-[3-(N,N-dimethylamino)propoxy]-benzimidazole**

15 The title compound was prepared by reacting the compound of Example 104 with 3-(N,N-dimethylamino)propyl chloride essentially as previously described. mp 142°C, NMR, IR, MS 543.

Analysis for $C_{29}H_{32}F_3N_3O_4$:

20 Theory: C, 64.08; H, 5.93; N, 7.73.

Found: C, 64.33; H, 5.78; N, 7.47.

Example 109

25 **Synthesis of 1-(2-trifluoromethylbenzyl)-2-(3,4,5-trimethoxyphenyl)-6-[3-(piperidin-1-yl)propoxy]benzimidazole**

30 The title compound was prepared by reacting the compound of Example 104 with 3-(piperidin-1-yl)propyl chloride essentially as previously described. mp 138°C, IR, NMR, MS. 584
Analysis for $C_{32}H_{36}F_3N_3O_4$:

Theory: C, 65.85; H, 6.22; N, 7.20.

Found: C, 65.74; H, 6.07; N, 7.35.

35

Example 110

Synthesis of 1-(2-trifluoromethylbenzyl)-2-(3,4,5-trimethoxyphenyl)-6-[2-(hexamethyleneimin-1-yl)ethoxy]benzimidazole

5 The title compound was prepared by reacting the compound of Example 104 with 2-(hexamethyleneimin-1-yl)ethyl chloride essentially as previously described. mp 156°C, IR, NMR, MS 583, 584. Analysis for C₃₂H₃₆F₃N₃O₄:

Theory: C, 65.85; H, 6.22; N, 7.20.

Found: C, 65.59; H, 5.98; N, 7.33.

10

Example 111

Synthesis of 1-(2-trifluoromethylbenzyl)-2-(3,4,5-trimethoxyphenyl)-6-[2-(pyrrolidin-1-yl)ethoxy]benzimidazole

15

The title compound was prepared by reacting the compound of Example 104 with 2-(pyrrolidin-1-yl)ethyl chloride essentially as previously described. mp 143°C, NMR, IR, MS 555.

Analysis for C₃₀H₃₂F₃N₃O₄:

20

Theory: C, 64.85; H, 5.80; N, 7.56.

Found: C, 64.93; H, 5.87; N, 7.54.

Example 112

25

Synthesis of 1-(2-trifluoromethylbenzyl)-2-(3,4,5-trimethoxyphenyl)-6-[2-(morpholin-4-yl)ethoxy]benzimidazole

30

The title compound was prepared by reacting the compound of Example 104 with 2-(morpholin-4-yl)ethyl chloride essentially as previously described. mp 175°C, NMR, IR, MS 572.

Analysis for C₃₀H₃₂F₃N₃O₅:

Theory: C, 63.04; H, 5.64; N, 7.35.

Found: C, 62.82; H, 5.74; N, 7.38.

35

Example 113

Synthesis of 1-(2-trifluoromethylbenzyl)-2-(3,4,5-trimethoxyphenyl)-6-[2-(N,N-diisopropylamino)ethoxy]benzimidazole

5 The title compound was prepared by reacting the compound of Example 104 with 2-(N,N-diisopropylamino)ethyl chloride essentially as previously described. mp 184°C, MS 585, NMR, IR.
Analysis for C₃₂H₃₈F₃N₃O₄:

Theory: C, 65.63; H, 6.54; N, 7.18.

Found: C, 65.67; H, 6.42; N, 7.35.

10

Example 114

Synthesis of 1-(2-bromobenzyl)-2-(3,4,5-trimethoxyphenyl)-6-hydroxybenzimidazole

15

The title compound was prepared essentially as described in Example 104 except that 2-bromobenzyl bromide was employed in place of 2-trifluoromethylbenzyl bromide. mp 208°C, NMR, IR, MS 468, 470.

20 Analysis for C₂₃H₂₁BrN₂O₄:

Theory: C, 58.86; H, 4.51; N, 5.97.

Found: C, 58.61; H, 4.81; N, 6.12.

Example 115

25

Synthesis of 1-(2-bromobenzyl)-2-(3,4,5-trimethoxyphenyl)-6-[2-(piperidin-1-yl)ethoxy]benzimidazole

30

The title compound was prepared by reacting the compound of Example 114 with 2-(piperidin-1-yl)ethyl chloride essentially as previously described. mp 145°C, NMR, MS 579, 581, IR.
Analysis for C₃₀H₃₄BrN₃O₄:

Theory: C, 62.07; H, 5.90; N, 7.24.

Found: C, 61.86; H, 5.91; N, 7.08.

35

Example 116

Synthesis of 1-(2-bromobenzyl)-2-(3,4,5-trimethoxyphenyl)-6-[2-(N,N-dimethylamino)propoxy]benzimidazole

5 The title compound was prepared by reacting the compound of Example 114 with 2-(N,N-dimethylamino)propyl chloride essentially as previously described. mp 152°C, NMR, IR, MS 553, 555.
Analysis for $C_{28}H_{32}BrN_3O_4$:

10 Theory: C, 60.65; H, 5.82; N, 7.58.
 Found: C, 60.85; H, 5.77; N, 7.44.

Example 117

15 **Synthesis of 1-(2-bromobenzyl)-2-(3,4,5-trimethoxyphenyl)-6-[2-(N,N-dimethylamino)ethoxy]benzimidazole**

20 The title compound was prepared by reacting the compound of Example 114 with 2-(N,N-dimethylamino)ethyl chloride essentially as previously described. mp 152°C, NMR, IR, MS 539, 541.
Analysis for $C_{27}H_{30}BrN_3O_4$:

 Theory: C, 60.00; H, 5.59; N, 7.77.
 Found: C, 59.83; H, 5.63; N, 7.54.

Example 118

25 **Synthesis of 1-(2-bromobenzyl)-2-(3,4,5-trimethoxyphenyl)-6-[3-(N,N-dimethylamino)propoxy]benzimidazole**

30 The title compound was prepared by reacting the compound of Example 114 with 3-(N,N-dimethylamino)propyl chloride essentially as previously described. mp 141°C, NMR, IR, MS 553, 555.
Analysis for $C_{28}H_{32}BrN_3O_4$:

 Theory: C, 60.65; H, 5.82; N, 7.58.
 Found: C, 60.49; H, 6.03; N, 7.34.

35

Example 119

Synthesis of 1-(2-bromobenzyl)-2-(3,4,5-trimethoxyphenyl)-6-[2-(N,N-diisopropylamino)ethoxy]benzimidazole

5 The title compound was prepared by reacting the compound of Example 114 with 2-(N,N-diisopropylamino)ethyl chloride essentially as previously described. MS 595, 597.

Analysis for $C_{31}H_{38}BrN_3O_4$:

Theory: C, 62.41; H, 6.42; N, 7.04.

10 Found: C, 62.48; H, 6.48; N, 7.03.

Example 120

15 **Synthesis of 1-(2-trifluoromethylbenzyl)-2-(3-methylphenyl)-6-hydroxybenzimidazole**

20 The title compound was prepared essentially as described in Example 104, *supra*, except that 3-methylbenzoyl chloride was employed instead of 3,4,5-trimethoxybenzoyl chloride. mp 233°C, MS 382, IR, NMR.

Analysis for $C_{22}H_{17}F_3N_2O$:

Theory: C, 69.10; H, 4.48; N, 7.33.

Found: C, 69.40; H, 4.49; N, 7.27.

25 **Example 121**

Synthesis of 1-(2-trifluoromethylbenzyl)-2-(3-methylphenyl)-6-[2-(piperidinyl-1-yl)ethoxy]benzimidazole

30 The title compound was prepared essentially as described in Example 105 except that the compound of Example 120 was reacted with 2-(piperidin-1-yl)ethyl chloride. mp 114°C, NMR, IR, MS 493.

Analysis for $C_{29}H_{30}F_3N_3O$:

Theory: C, 70.57; H, 6.13; N, 8.51.

35 Found: C, 70.77; H, 6.22; N, 8.50.

Example 122

Synthesis of 1-(2-trifluoromethylbenzyl)-2-(3-methylphenyl)-6-[2-(N,N-dimethylamino)ethoxy]benzimidazole

5

The title compound was prepared essentially as described in Example 107 except that the compound of Example 120 was reacted with 2-(N,N-dimethylamino)ethyl chloride. mp 93°C, NMR, IR, MS 453. Analysis for $C_{26}H_{26}F_3N_3O$:

10 Theory: C, 68.86; H, 5.78; N, 9.26.
Found: C, 69.12; H, 5.79; N, 9.34.

Example 123

15 Synthesis of 1-(2-trifluoromethylbenzyl)-2-(3-methylphenyl)-6-[2-(N,N-diisopropylamino)ethoxy]benzimidazole

20 The title compound was prepared essentially as described in Example 113 except that the compound of Example 120 was reacted with 2-(N,N-diisopropylamino)ethyl chloride. MS 510. Analysis for $C_{30}H_{34}F_3N_3O$:

Theory: C, 70.71; H, 6.72; N, 8.25.
Found: C, 70.48; H, 6.59; N, 8.26.

25 Example 124

Synthesis of 1-(2-trifluoromethylbenzyl)-2-(3-methylphenyl)-6-[3-(N,N-dimethylamino)propoxy]benzimidazole

30 The title compound was prepared essentially as described in Example 106 except that the compound of Example 120 was reacted with 3-(N,N-dimethylamino)propyl chloride. mp 74°C, NMR, IR, MS 468.

Analysis for $C_{27}H_{28}F_3N_3O$:

35 Theory: C, 69.36; H, 6.04; N, 8.99.
Found: C, 69.52; H, 6.10; N, 9.03.

Example 125

5 **Synthesis of 1-(2-trifluoromethylbenzyl)-2-(3-methylphenyl)-6-[1-methyl-
2-(N,N-dimethylamino)ethoxy]benzimidazole**

10 The title compound was prepared essentially as described
above except that the compound of Example 120 was reacted with 1-
methyl-2-(N,N-dimethylamino)ethyl chloride, yielding the title product
as an oil.

Example 126

15 **Synthesis of 1-(2-bromobenzyl)-2-(3-methylphenyl)-6-
hydroxybenzimidazole**

20 The title compound was prepared essentially as described
in Example 114, *supra*, except that 3-methylbenzoyl chloride was
employed instead of 3,4,5-trimethoxybenzoyl chloride. mp 218°C, NMR,
IR, MS 392, 394.

Analysis for $C_{21}H_{17}BrN_2O$:

Theory: C, 64.13; H, 4.36; N, 7.12.

Found: C, 64.23; H, 4.51; N, 6.93.

25 Example 127

**Synthesis of 1-(2-bromobenzyl)-2-(3-methylphenyl)-6-[2-(piperidinyl-1-
yl)ethoxy]benzimidazole**

30 The title compound was prepared essentially as described
in Example 115 except that the compound of Example 126 was reacted
with 2-(piperidin-1-yl)ethyl chloride. mp 107°C, NMR, IR, MS 503, 505.
Analysis for $C_{28}H_{30}BrN_3O$:

Theory: C, 66.67; H, 5.99; N, 8.33.

35 Found: C, 66.97; H, 6.12; N, 8.19.

Example 128**Synthesis of 1-(2-bromobenzyl)-2-(3-methylphenyl)-6-[2-(N,N-dimethylamino)ethoxy]benzimidazole**

5

The title compound was prepared essentially as described in Example 117 except that the compound of Example 126 was reacted with 2-(N,N-dimethylamino)ethyl chloride. mp 71°C, NMR, IR, MS 464, 466.

10 **Analysis for C₂₅H₂₆BrN₃O:**

Theory: C, 64.66; H, 5.64; N, 9.05.

Found: C, 64.58; H, 5.58; N, 9.04.

Example 130

15

Synthesis of 1-(2-bromobenzyl)-2-(3-methylphenyl)-6-[3-(N,N-dimethylamino)propoxy]benzimidazole

The title compound was prepared essentially as described in Example 116 except that the compound of Example 126 was reacted with 3-(N,N-dimethylamino)propyl chloride. MS 479.

Analysis for C₂₆H₂₈BrN₃O:

Theory: C, 65.27; H, 5.90; N, 8.78.

Found: C, 64.99; H, 5.85; N, 8.66.

25

Example 131**Synthesis of 1-(2-bromobenzyl)-2-(3-methylphenyl)-6-[1-methyl-2-(N,N-dimethylamino)ethoxy]benzimidazole**

30

The title compound was prepared essentially as described above except that the compound of Example 126 was reacted with 1-methyl-2-(N,N-dimethylamino)ethyl chloride.

35

Example 132

Synthesis of 1-(2-trifluoromethylbenzyl)-2-(3,4-dimethylphenyl)-6-hydroxybenzimidazole

5 The title compound was prepared essentially as described in Example 104 except that 3,4-dimethylbenzoyl chloride was employed instead of 3,4,5-trimethoxybenzoyl chloride. mp 178°C, NMR, IR, MS 396.

Analysis for $C_{23}H_{19}F_3N_2O$:

Theory: C, 69.69; H, 4.83; N, 7.07.
10 Found: C, 69.40; H, 4.87; N, 6.90.

The following compounds were prepared essentially as described *supra*, except that the compound of Example 132 was employed as a starting material.

15

Example 133

1-(2-trifluoromethylbenzyl)-2-(3,4-dimethylphenyl)-6-[2-(piperidin-1-yl)ethoxy]benzimidazole. mp 131°C, NMR, MS 507, IR.
20 Analysis for $C_{30}H_{32}F_3N_3O$:

Theory: C, 70.99; H, 6.35; N, 8.28.
Found: C, 70.70; H, 6.23; N, 8.42.

Example 134

25

1-(2-trifluoromethylbenzyl)-2-(3,4-dimethylphenyl)-6-[2-(N,N-dimethylamino)ethoxy]benzimidazole. mp 87°C, MS 467, NMR, IR.
Analysis for $C_{27}H_{28}F_3N_3O$:

Theory: C, 69.36; H, 6.04; N, 8.99.
30 Found: C, 69.42; H, 6.01; N, 8.91.

Example 135

1-(2-trifluoromethylbenzyl)-2-(3,4-dimethylphenyl)-6-[2-(N,N-diisopropylamino)ethoxy]benzimidazole. mp 121°C, NMR, IR, MS 524.
35 Analysis for $C_{31}H_{36}F_3N_3O$:

Theory: C, 71.11; H, 6.93; N, 8.03.

Found: C, 71.34; H, 6.96; N, 8.26.

Example 136

5

1-(2-trifluoromethylbenzyl)-2-(3,4-dimethylphenyl)-6-[2-(N,N-dimethylamino)propoxy]benzimidazole.

MS 481.

Analysis for C₂₈H₃₀F₃N₃O:

10 Theory: C, 69.84; H, 6.28; N, 8.73.

Found: C, 70.24; H, 6.33; N, 8.55.

Example 136A

15 1-(2-trifluoromethylbenzyl)-2-(3,4-dimethylphenyl)-6-[1-methyl-2-(N,N-dimethylamino)ethoxy]benzimidazole

MS 481.

Analysis for C₂₈H₃₀F₃N₃O:

Theory: C, 69.84; H, 6.28; N, 8.73.

20 Found: C, 69.61; H, 6.35; N, 8.50.

Example 137

1-(2-bromomethylbenzyl)-2-(3,4-dimethylphenyl)-6-hydroxybenzimidazole

25

The title compound was prepared essentially as described in Example 114, *supra*, except that 3,4-dimethylbenzoyl chloride was employed instead of 3,4,5-trimethoxybenzoyl chloride. mp 213°C, MS 406, 408, NMR, IR.

30 Analysis for C₂₂H₁₉BrN₂O:

Theory: C, 64.56; H, 5.17; N, 6.84.

Found: C, 64.76; H, 4.95; N, 6.62.

35 The following compounds were prepared essentially as described *supra*, except that the compound of Example 138 was employed as a starting material.

Example 138

5 1-(2-trifluoromethylbenzyl)-2-(3,4-dimethylphenyl)-6-[3-(N,N-dimethylamino)propoxy]benzimidazole
Analysis for C₂₇H₃₀BrN₃O:

Theory: C, 65.85; H, 6.14; N, 8.53.
Found: C, 66.12; H, 6.20; N, 8.49.

10

Example 139

1-(2-bromobenzyl)-2-(3,4-dimethylphenyl)-6-[2-(piperidin-1-yl)ethoxy]benzimidazole. mp 137°C, NMR, IR, MS 517, 519.
Analysis for C₂₉H₃₂BrN₃O:

15 Theory: C, 67.18; H, 6.72; N, 8.10.
Found: C, 67.45; H, 6.30; N, 8.01.

Example 140

20 1-(2-bromobenzyl)-2-(3,4-dimethylphenyl)-6-[2-(N,N-dimethylamino)ethoxy]benzimidazole. mp 102°C, IR, NMR, MS 478, 479, 480.

Analysis for C₂₆H₂₈BrN₃O:

25 Theory: C, 65.27; H, 5.90; N, 8.78.
Found: C, 65.43; H, 5.88; N, 8.75.

Example 141

30 1-(2-bromobenzyl)-2-(3,4-dimethylphenyl)-6-[2-(N,N-diisopropylamino)ethoxy]benzimidazole
MS 533, 535.

Analysis for C₃₀H₃₆BrN₃O:

35 Theory: C, 67.41; H, 6.79; N, 7.86.
Found: C, 67.36; H, 6.60; N, 7.93.

Example 142

1-(2-bromobenzyl)-2-(3,4-dimethylphenyl)-6-[2-(N,N-dimethylamino)propoxy]benzimidazole. MS 491, 493.
Analysis for C₂₇H₃₀BrN₃O:

5 Theory: C, 65.85; H, 6.14; N, 8.53.
 Found: C, 66.07; H, 6.18; N, 8.54.

Example 142A

10 1-(2-bromobenzyl)-2-(3,4-dimethylphenyl)-6-[1-methyl-2-(N,N-dimethylamino)ethoxy]benzimidazole. MS 491, 493.
Analysis for C₂₇H₃₀BrN₃O:

15 Theory: C, 65.85; H, 6.14; N, 8.53.
 Found: C, 65.74; H, 6.20; N, 8.32.

Example 143

1-(2-bromobenzyl)-2-(3,4-dimethylphenyl)-6-[3-(N,N-dimethylamino)propoxy]benzimidazole. MS 491, 493.
20 Analysis for C₁₁H₁₄N₂O₄S:

25 Theory: C, 65.85; H, 6.14; N, 8.53.
 Found: C, 66.12; H, 6.20; N, 8.49.

Example 145

25 1-(2-bromomethylbenzyl)-2-(3,5-dimethylphenyl)-6-hydroxybenzimidazole

The title compound was prepared essentially as described in Example 114, *supra*, except that 3,5-dimethylbenzoyl chloride was employed instead of 3,4,5-trimethoxybenzoyl chloride. mp 213°C, MS 406, 408, NMR, IR.
30 Analysis for C₂₂H₁₉BrN₂O:

35 Theory: C, 64.88; H, 4.70; N, 6.88.
 Found: C, 64.74; H, 4.80; N, 7.01.

The following compounds were prepared essentially as described *supra*, except that the compound of Example 145 was employed as a starting material.

5

Example 146

1-(2-bromobenzyl)-2-(3,5-dimethylphenyl)-6-[2-(piperidin-1-yl)ethoxy]benzimidazole

IR, NMR, MS 517, 519, mp 112°C.

10 Analysis for $C_{29}H_{32}BrN_3 \cdot 0.5 H_2O$:

Theory: C, 66.03; H, 6.31; N, 7.97.

Found: C, 66.17; H, 6.50; N, 7.46.

15

Example 147

1-(2-bromobenzyl)-2-(3,5-dimethylphenyl)-6-[2-(N,N-dimethylamino)ethoxy]benzimidazole

MS 477, 479.

Analysis for $C_{26}H_{28}BrN_3O \cdot H_2O$:

20 Theory: C, 62.90; H, 6.09; N, 8.46.

Found: C, 63.09; H, 5.95; N, 8.45.

Example 148

25 1-(2-bromobenzyl)-2-(3,5-dimethylphenyl)-6-[1-methyl-2-(N,N-dimethylamino)ethoxy]benzimidazole. mp 78°C, NMR, IR, MS 491, 493. Analysis for $C_{27}H_{30}BrN_3O$:

Theory: C, 65.85; H, 6.14; N, 8.53.

Found: C, 66.05; H, 6.15; N, 8.80.

30

Example 149

1-(2-bromobenzyl)-2-(3,5-dimethylphenyl)-6-[2-(N,N-diisopropylamino)ethoxy]benzimidazole

35 MS 534, 536.

Analysis for $C_{30}H_{36}BrN_3O$:

Theory: C, 67.41; H, 6.79; N, 7.86.
Found: C, 67.34; H, 6.87; N, 7.62.

Example 150

5

1-(2-bromobenzyl)-2-(3,5-dimethylphenyl)-6-[3-(N,N-dimethylamino)propoxy]benzimidazole. MS 491, 493.
Analysis for C₂₇H₃₀BrN₃O:

Theory: C, 65.85; H, 6.14; N, 8.53.
10 Found: C, 65.68; H, 6.19; N, 8.53.

Example 151

15

1-phenyl-2-[3-[2-(piperidin-1-yl)ethoxy]phenyl]-benzimidazole

The title compound was prepared by reacting the compound of Example 34 with 2-(piperidin-1-yl)ethyl chloride in acetone and potassium carbonate as previously described. mp 68°C, IR, NMR, MS 397.

20 Analysis for C₂₆H₂₇N₃O:

Theory: C, 78.56; H, 6.85; N, 10.57.
Found: C, 78.41; H, 6.90; N, 10.45.

Example 152

25

1-phenyl-2-[4-[2-(piperidin-1-yl)ethoxy]phenyl]-benzimidazole

The title compound was prepared by reacting the compound of Example 29 with 2-(piperidin-1-yl)ethyl chloride in acetone and potassium carbonate as previously described. mp 107°C, NMR, MS 397.
Analysis for C₂₆H₂₇N₃O:

Theory: C, 78.56; H, 6.85; N, 10.57.
Found: C, 78.79; H, 7.12; N, 10.51.

35

Example 153

1-phenyl-2-[4-[3-(piperidin-1-yl)propoxy]phenyl]-benzimidazole

5 The title compound was prepared by reacting the compound of Example 29 with 3-(piperidin-1-yl)propyl chloride in acetone and potassium carbonate as previously described. mp 86°C, NMR, MS 412. Analysis for C₂₇H₂₉N₃O:

Theory: C, 78.80; H, 7.10; N, 10.21.

Found: C, 79.01; H, 7.18; N, 10.20.

10

Example 154**Synthesis of 1-phenyl-2-(3,4-dimethylphenyl)-6-hydroxybenzimidazole**

15 The title compound was prepared by first reacting 1-chloro-3,4-dinitrobenzene (100 g, 0.50 mole) with aniline (140 ml, 1.54 moles) in ethanol (95%, 550 ml). This reaction mixture was stirred at room temperature for about 72 hours. The resulting 1-chloro-3-phenylamino-4-nitrobenzene was purified by first filtering the orange crystals, followed by washing with hexanes. The crystals were then dried at 80°C
20 for about 4 hours. Additional product was recovered from the hexanes filtrate by recrystallizing from ethanol.

25 The 1-chloro-3-phenylamino-4-nitrobenzene was then reacted with two molar equivalents of sodium methoxide, the sodium methoxide being prepared essentially as described in Kottenhahn, *et al.*, Journal of Organic Chemistry, 28:3114 (1963). Metallic sodium (5.0 g, 217 mmol) was added slowly to methanol (400 ml). After all of the sodium had gone into solution, the 1-chloro-3-phenylamino-4-nitrobenzene was added and the red-orange solution was heated to reflux and maintained at that temperature overnight. The gold crystals
30 of 1-methoxy-3-phenylamino-4-nitrobenzene were recovered by filtration, washed with water (2 liters) and dried in vacuo.

35 The nitro group of the above-described intermediate was then reduced to an amino group by catalytic hydrogenation using a palladium on activated carbon catalyst, essentially as previously described, resulting in 3-phenylamino-4-methoxyaniline which was then reacted with 3,4-dimethylbenzoyl chloride as previously described. This

intermediate was then cyclized to the corresponding benzimidazole with phosphorous oxychloride as previously described to yield 1-phenyl-2-(3,4-dimethylphenyl)-6-methoxybenzimidazole.

This intermediate was then reacted with hydrobromic acid 5 (48%) and glacial acetic acid under nitrogen atmosphere to cleave the methoxy group from the 6-position of the benzimidazole. The resulting title compound was purified by adding the reaction mixture to one liter of water and extracting with methylene chloride (3 x 500 ml). The 10 organic fractions were combined, dried over magnesium sulfate and the solvents were removed in vacuo to yield reddish solid crystals. The crystals were washed with water (3 x 250 ml) to remove excess hydrobromic acid and then dried, followed by washing with diethyl ether (2 x 250 ml) and drying in vacuo. mp 251°C, IR, NMR, MS 314.

Analysis for $C_{21}H_{18}N_2O$:

15 Theory: C, 80.23; H, 5.77; N, 8.91.
 Found: C, 79.98; H, 5.77; N, 8.94.

Example 155

20 1-phenyl-2-(3,4-dimethylphenyl)-6-[2-(piperidin-1-yl)ethoxy]benzimidazole

The title compound was prepared by reacting the compound 25 of Example 154, supra, with 2-(piperidin-1-yl)ethyl chloride as previously described. NMR, IR, MS 425, mp 111°C.
Analysis for $C_{28}H_{31}N_3O \cdot 0.5 H_2O$:

Theory: C, 77.39; H, 7.42; N, 9.67.
Found: C, 77.38; H, 7.24; N, 10.36.

30 The following compounds were prepared essentially as described above:

Example 156

35 1-Benzyl-2-phenylbenzimidazole

Example 157

1-(1-Diethylaminopent-4-yl)-2-(3-nitrophenyl)benzimidazole

5

Example 158

1-(1-Diethylaminopent-4-yl)-2-(4-methoxyphenyl)-benzimidazole

10

Example 159

1-(1-Dimethylaminoethyl)-2-phenylbenzimidazole

15

Example 160

15 1-(1-Dimethylaminopropyl)-2-benzylbenzimidazole

Example 161

20 1-(4-chlorophenylmethyl)-2-(4-chlorophenylmethyl)-benzimidazole. mp 89-90°C.

Example 162

25 1-phenyl-2-(4-chlorophenyl)-6-methoxybenzimidazole. mp 171-172.5°C.

Example 163

30 1-phenyl-2-(4-chlorophenyl)-5-(1-ethylaminoethyl)-benzimidazole, (Z)-2-butenedioic acid salt. mp 228°C.

Example 164

35 1-phenyl-2-(4-chlorophenyl)-6-chlorobenzimidazole. mp 210-212°C.

Example 165

- 92 -

1-phenyl-2-(4-chlorophenyl)-6-(imidazol-1-yl)benzimidazole. mp 223°C.

Example 166

5 1-phenyl-2-(4-chlorophenyl)-5-nitrobenzimidazole. mp 194°C.

Example 167

10 1-phenyl-2-(4-chlorophenyl)-6-hydroxyethylamino-benzimidazole. mp 225°C.

Example 168

15 1-phenyl-2-(4-chlorophenyl)-5-(1-aminoethyl)benzimidazole, (Z)-2-
butenedioic acid salt. mp 206°C.

Example 169

20 1-phenyl-2-(4-chlorophenyl)-6-(N-isopropylcarbonyl-N-
butylamino)benzimidazole. bp 213-220°C.

Example 170

25 1-phenyl-2-(4-chlorophenyl)-5-acetylbenzimidazole. mp 159°C.

Example 171

1-phenyl-2-(4-chlorophenyl)-5-(2-hydroxyethyl)benzimidazole. mp 165°C.

30 Example 172

1-phenyl-2-(4-chlorophenyl)-6-[2-(piperidin-1-yl)ethoxy]benzimidazole.
mp 138-140.

35 Example 173

1-phenyl-2-(4-chlorophenyl)-6-[3-(N,N-dimethylamino)-propoxy]benzimidazole. mp 126°C.

Example 174

5

1-phenyl-2-(4-hydroxyphenyl)-6-hydroxybenzimidazole, hydrochloride. mp 212°C.

10 The other compounds of Formula I may be prepared
essentially as described above, employing corresponding starting
materials.

15 The biological efficacy of a compound believed to be effective
as a tachykinin receptor antagonist may be confirmed by employing an
initial screening assay which rapidly and accurately measured the
binding of the tested compound to known NK-1 and NK-2 receptor sites.
Assays useful for evaluating tachykinin receptor antagonists are well
known in the art. See, e.g., J. Jukic, et al., Life Sciences, 49:1463-1469
20 (1991); N. Kucharczyk, et al., Journal of Medicinal Chemistry,
36:1654-1661 (1993); N. Rouissi, et al., Biochemical and Biophysical
Research Communications, 176:894-901 (1991).

NK-1 Receptor Binding Assay

25 Radioreceptor binding assays were performed using a
derivative of a previously published protocol. D.G. Payan, et al., Journal
of Immunology, 133:3260-3265 (1984). In this assay an aliquot of IM9
cells (1×10^6 cells/tube in RPMI 1604 medium supplemented with 10%
30 fetal calf serum) was incubated with 20 pM 125 I-labeled substance P in
the presence of increasing competitor concentrations for 45 minutes at
4°C.

The IM9 cell line is a well-characterized cell line which is
readily available to the public. See, e.g., Annals of the New York
Academy of Science, 190: 221-234 (1972); Nature (London), 251:443-444
35 (1974); Proceedings of the National Academy of Sciences (USA), 71:84-88

(1974). These cells were routinely cultured in RPMI 1640 supplemented with 50 μ g/ml gentamicin sulfate and 10% fetal calf serum.

5 The reaction was terminated by filtration through a glass fiber filter harvesting system using filters previously soaked for 20 minutes in 0.1% polyethylenimine. Specific binding of labeled substance P was determined in the presence of 20 nM unlabeled ligand.

10 Many of the compounds employed in the methods of the present invention are also effective antagonists of the NK-2 receptor.

NK-2 Receptor Binding Assay

15 The CHO-hNK-2R cells, a CHO-derived cell line transformed with the human NK-2 receptor, expressing about 400,000 such receptors per cell, were grown in 75 cm^2 flasks or roller bottles in minimal essential medium (alpha modification) with 10% fetal bovine serum. The gene sequence of the human NK-2 receptor is given in N.P. Gerard, *et al.*, *Journal of Biological Chemistry*, 265:20455-20462 (1990).

20 For preparation of membranes, 30 confluent roller bottle cultures were dissociated by washing each roller bottle with 10 ml of Dulbecco's phosphate buffered saline (PBS) without calcium and magnesium, followed by addition of 10 ml of enzyme-free cell dissociation solution (PBS-based, from Specialty Media, Inc.). After an additional 15 minutes, the dissociated cells were pooled and centrifuged 25 at 1,000 RPM for 10 minutes in a clinical centrifuge. Membranes were prepared by homogenization of the cell pellets in 300 ml 50 mM Tris buffer, pH 7.4 with a Tekmar® homogenizer for 10-15 seconds, followed by centrifugation at 12,000 RPM (20,000 x g) for 30 minutes using a Beckman JA-14® rotor. The pellets were washed once using the above 30 procedure. and the final pellets were resuspended in 100-120 ml 50 mM Tris buffer, pH 7.4, and 4 ml aliquots stored frozen at -70°C. The protein concentration of this preparation was 2 mg/ml.

35 For the receptor binding assay, one 4-ml aliquot of the CHO-hNK-2R membrane preparation was suspended in 40 ml of assay buffer containing 50 mM Tris, pH 7.4, 3 mM manganese chloride, 0.02% bovine serum albumin (BSA) and 4 μ g/ml chymostatin. A 200 μ l volume

of the homogenate (40 µg protein) was used per sample. The radioactive ligand was [¹²⁵I]iodohistidyl-neurokinin A (New England Nuclear, NEX-252), 2200 Ci/mmol. The ligand was prepared in assay buffer at 20 nCi per 100 µl; the final concentration in the assay was 20 pM.

5 Non-specific binding was determined using 1 µM eledoisin. Ten concentrations of eledoisin from 0.1 to 1000 nM were used for a standard concentration-response curve.

10 All samples and standards were added to the incubation in 10 µl dimethylsulfoxide (DMSO) for screening (single dose) or in 5 µl DMSO for IC₅₀ determinations. The order of additions for incubation was 190 or 195 µl assay buffer, 200 µl homogenate, 10 or 5 µl sample in DMSO, 100 µl radioactive ligand. The samples were incubated 1 hr at room temperature and then filtered on a cell harvester through filters which had been presoaked for two hours in 50 mM Tris buffer, pH 7.7, 15 containing 0.5% BSA. The filter was washed 3 times with approximately 3 ml of cold 50 mM Tris buffer, pH 7.7. The filter circles were then punched into 12 x 75 mm polystyrene tubes and counted in a gamma counter.

20 The compounds of Formula I are useful in treating sleep apnea. The effectiveness of a compound employed in the present invention may be demonstrated using standard techniques. United States Patent 5,422,374, issued June 6, 1995, the entire contents of which are herein incorporated by reference, describes a typical study to 25 examine the effectiveness of a compound in treating sleep apnea.

Sleep Study Example 1

30 Ten patients of sleep apnea are given a soft capsule containing 10 mg of (R)-3-(1H-indol-3-yl)-1-[N-(2-methoxybenzyl)acetylamino]-2-[N-(2-(4-(piperidin-1-yl)piperidin-1-yl)acetyl)amino]propane dihydrochloride trihydrate before bed. Observation of the patients during sleep reveals no apneic symptoms. Moreover, no feelings of mailaise in daytime are observed.

Sleep Study Example 2

5 The patients who have been diagnosed with sleep apnea are given soft capsules, each containing 10 mg of (R)-3-(1H-indol-3-yl)-1-[N-(2-methoxybenzyl)acetyl]amino]-2-[N-(2-(4-(piperidin-1-yl)piperidin-1-yl)acetyl)amino]propane dihydrochloride trihydrate at a dose of one capsule after supper for period of days. Clinical symptoms of the patients are observed, and apnea index (times/hour) are also measured before and after administration.

10

10 While it is possible to administer a compound employed in the methods of this invention directly without any formulation, the compounds are usually administered in the form of pharmaceutical compositions comprising a pharmaceutically acceptable excipient and 15 at least one active ingredient. These compositions can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal. Many of the compounds employed in the methods of this invention are effective as both injectable and oral compositions. Such compositions are prepared in a manner 20 well known in the pharmaceutical art and comprise at least one active compound. See, e.g., REMINGTON'S PHARMACEUTICAL SCIENCES, (16th ed. 1980).

25 In making the compositions employed in the present invention the active ingredient is usually mixed with an excipient, diluted by an excipient or enclosed within such a carrier which can be in the form of a capsule, sachet, paper or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, 30 powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing for example up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

35 In preparing a formulation, it may be necessary to mill the active compound to provide the appropriate particle size prior to

combining with the other ingredients. If the active compound is substantially insoluble, it ordinarily is milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size is normally adjusted by milling to provide a 5 substantially uniform distribution in the formulation, e.g. about 40 mesh.

Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, 10 microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxybenzoates; sweetening agents; and 15 flavoring agents. The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art.

The compositions are preferably formulated in a unit 20 dosage form, each dosage containing from about 0.05 to about 100 mg, more usually about 1.0 to about 30 mg, of the active ingredient. The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the 25 desired therapeutic effect, in association with a suitable pharmaceutical excipient.

The active compounds are generally effective over a wide dosage range. For examples, dosages per day normally fall within the 30 range of about 0.01 to about 30 mg/kg of body weight. In the treatment of adult humans, the range of about 0.1 to about 15 mg/kg/day, in single or divided dose, is especially preferred. However, it will be understood that the amount of the compound actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual 35 compound or compounds administered, the age, weight, and response of the individual patient, and the severity of the patient's symptoms, and

- 98 -

therefore the above dosage ranges are not intended to limit the scope of the invention in any way. In some instances dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any
5 harmful side effect, provided that such larger doses are first divided into several smaller doses for administration throughout the day.

Formulation Preparation 1

10 Hard gelatin capsules containing the following ingredients are prepared:

	<u>Ingredient</u>	<u>Quantity</u> (mg/capsule)
15	Active Ingredient(s)	30.0
	Starch	305.0
	Magnesium stearate	5.0
20		

The above ingredients are mixed and filled into hard gelatin capsules in 340 mg quantities.

- 99 -

Formulation Preparation 2

A tablet formula is prepared using the ingredients below:

	<u>Ingredient</u>	<u>Quantity</u> <u>(mg/tablet)</u>
5	Active Ingredient(s)	25.0
10	Cellulose, microcrystalline	200.0
10	Colloidal silicon dioxide	10.0
	Stearic acid 5.0	
15	The components are blended and compressed to form tablets, each weighing 240 mg.	

- 100 -

Formulation Preparation 3

A dry powder inhaler formulation is prepared containing the following components:

5

	<u>Ingredient</u>	<u>Weight %</u>
	Active Ingredient(s)	5

	Lactose	95
--	---------	----

10

The active mixture is mixed with the lactose and the mixture is added to a dry powder inhaling appliance.

Formulation Preparation 4

Tablets, each containing 30 mg of active ingredient, are prepared as follows:

	<u>Ingredient</u>	<u>Quantity</u> (mg/tablet)
5	Active Ingredient(s)	30.0 mg
10	Starch	45.0 mg
	Microcrystalline cellulose	35.0 mg
15	Polyvinylpyrrolidone (as 10% solution in water)	4.0 mg
	Sodium carboxymethyl starch	4.5 mg
20	Magnesium stearate	0.5 mg
	Talc	<u>1.0 mg</u>
	Total	120 mg

25 The active ingredient, starch and cellulose are passed through a No. 20 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders, which are then passed through a 16 mesh U.S. sieve. The granules so produced are dried at 50-60°C and passed through a 16 mesh U.S. sieve. The 30 sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 30 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 120 mg.

Formulation Preparation 5

Capsules, each containing 40 mg of medicament are made as follows:

5

	<u>Ingredient</u>	<u>Quantity</u> (mg/capsule)
	Active Ingredient(s)	40.0 mg
10	Starch	109.0 mg
	Magnesium stearate	<u>1.0 mg</u>
	Total	150.0 mg

15

The active ingredient, cellulose, starch, and magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 150 mg quantities.

20

Formulation Preparation 6

Suppositories, each containing 25 mg of active ingredient are made as follows:

25

	<u>Ingredient</u>	<u>Amount</u>
	Active Ingredient(s)	25 mg
	Saturated fatty acid glycerides to	2,000 mg

30

The active ingredient(s) is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2.0 g capacity and allowed to cool.

35

Formulation Preparation 7

Suspensions, each containing 50 mg of medicament per 5.0 ml dose are made as follows:

	<u>Ingredient</u>	<u>Amount</u>
5	Active Ingredient(s)	50.0 mg
10	Xanthan gum	4.0 mg
	Sodium carboxymethyl cellulose (11%)	
	Microcrystalline cellulose (89%)	50.0 mg
15	Sucrose	1.75 g
	Sodium benzoate	10.0 mg
	Flavor and Color	q.v.
20	Purified water to	5.0 ml

The medicament, sucrose and xanthan gum are blended, passed through a No. 10 mesh U.S. sieve, and then mixed with a previously made solution of the microcrystalline cellulose and sodium carboxymethyl cellulose in water. The sodium benzoate, flavor, and color are diluted with some of the water and added with stirring. Sufficient water is then added to produce the required volume.

- 104 -

Formulation Preparation 8

Capsules, each containing 15 mg of medicament, are made as follows:

5

	<u>Ingredient</u>	<u>Quantity</u> (mg/capsule)
	Active Ingredient(s)	15.0 mg
10	Starch	407.0 mg
	Magnesium stearate	<u>3.0 mg</u>
	Total	425.0 mg

15

The active ingredient(s), cellulose, starch, and magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 425 mg quantities.

20

Formulation Preparation 9

An intravenous formulation may be prepared as follows:

25

	<u>Ingredient</u>	<u>Quantity</u>
	Active Ingredient(s)	250.0 mg
	Isotonic saline	1000 ml

30

- 105 -

Formulation Preparation 10

A topical formulation may be prepared as follows:

	<u>Ingredient</u>	<u>Quantity</u>
5	Active Ingredient(s)	1-10 g
	Emulsifying Wax	30 g
10	Liquid Paraffin	20 g
	White Soft Paraffin	to 100 g

15 The white soft paraffin is heated until molten. The liquid paraffin and emulsifying wax are incorporated and stirred until dissolved. The active ingredient is added and stirring is continued until dispersed. The mixture is then cooled until solid.

Formulation Preparation 11

Sublingual or buccal tablets, each containing 10 mg of active ingredient, may be prepared as follows:

5

	<u>Ingredient</u>	<u>Quantity</u> <u>Per Tablet</u>
	Active Ingredient(s)	10.0 mg
10	Glycerol	210.5 mg
	Water	143.0 mg
	Sodium Citrate	4.5 mg
15	Polyvinyl Alcohol	26.5 mg
	Polyvinylpyrrolidone	<u>15.5 mg</u>
	Total	410.0 mg

20

The glycerol, water, sodium citrate, polyvinyl alcohol, and polyvinylpyrrolidone are admixed together by continuous stirring and maintaining the temperature at about 90°C. When the polymers have gone into solution, the solution is cooled to about 50-55°C and the medicament is slowly admixed. The homogenous mixture is poured into forms made of an inert material to produce a drug-containing diffusion matrix having a thickness of about 2-4 mm. This diffusion matrix is then cut to form individual tablets having the appropriate size.

30

Another preferred formulation employed in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. See, e.g., U.S. Patent 5,023,252, issued June 11, 1991, herein incorporated by

35

reference. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

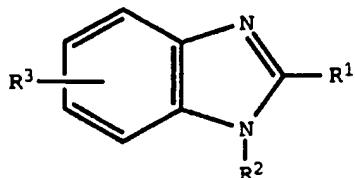
Frequently, it will be desirable or necessary to introduce the pharmaceutical composition to the brain, either directly or indirectly.

5 Direct techniques usually involve placement of a drug delivery catheter into the host's ventricular system to bypass the blood-brain barrier. One such implantable delivery system, used for the transport of biological factors to specific anatomical regions of the body, is described in U.S. Patent 5,011,472, issued April 30, 1991, which is herein incorporated by reference.

10 Indirect techniques, which are generally preferred, usually involve formulating the compositions to provide for drug latentiation by the conversion of hydrophilic drugs into lipid-soluble drugs or prodrugs. Latentiation is generally achieved through blocking of the hydroxy, carbonyl, sulfate, and primary amine groups present on the drug to render the drug more lipid soluble and amenable to transportation across the blood-brain barrier. Alternatively, the delivery of hydrophilic drugs may be enhanced by intra-arterial infusion of hypertonic solutions which can transiently open the blood-brain barrier.

We Claim:

1. A method for the treatment or prevention of sleep apnea in a mammal which comprise administering to a mammal in
 5 need thereof an effective amount of a compound of the formula



wherein:

10 R¹ is hydrogen, C₁-C₁₂ alkyl, C₁-C₆ alkoxy, phenyl, C₃-C₈ cycloalkyl, naphthyl, heterocyclic, unsaturated heterocyclic, phenyl-(C₁-C₆ alkylidenyl)-, naphthyl-(C₁-C₆ alkylidenyl)-, heterocyclic-(C₁-C₆ alkylidenyl)-, unsaturated heterocyclic-(C₁-C₆ alkylidenyl)-, phenyl-(C₁-C₆ alkoxy)-, naphthyl-(C₁-C₆ alkoxy)-, heterocyclic-(C₁-C₆ alkoxy)-, or unsaturated heterocyclic-(C₁-C₆ alkoxy)-,

15 any one of which phenyl, naphthyl, heterocyclic, C₃-C₈ cycloalkyl, or unsaturated heterocyclic groups may be optionally substituted with one, two, or three moieties independently selected from group consisting of heterocyclic-(C₁-C₆ alkylidenyl)-, unsaturated heterocyclic-(C₁-C₆ alkylidenyl)-, hydroxy, halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, trifluoromethyl, nitro, amino, cyano, C₁-C₆ alkylamino, and C₁-C₆ alkylthio;

20 R² is hydrogen, C₁-C₁₂ alkyl, C₁-C₆ alkoxy, phenyl, C₃-C₈ cycloalkyl, naphthyl, heterocyclic, unsaturated heterocyclic, phenyl-(C₁-C₆ alkylidenyl)-, naphthyl-(C₁-C₆ alkylidenyl)-, heterocyclic-(C₁-C₆ alkylidenyl)-, unsaturated

25

30

heterocyclic-(C₁-C₆ alkylidenyl)-, phenyl-(C₁-C₆ alkoxy)-, naphthyl-(C₁-C₆ alkoxy)-, heterocyclic-(C₁-C₆ alkoxy)-, or unsaturated heterocyclic-(C₁-C₆ alkoxy)-,

5 any one of which phenyl, naphthyl, heterocyclic, C₃-C₈ cycloalkyl, or unsaturated heterocyclic groups
may be optionally substituted with one, two, or three
moieties independently selected from group consisting
of phenyl-(C₁-C₆ alkylidenyl)-, naphthyl-(C₁-C₆ alkylidenyl)-, heterocyclic-(C₁-C₆ alkylidenyl)-,
10 unsaturated heterocyclic-(C₁-C₆ alkylidenyl)-, phenyl-(C₁-C₆ alkoxy)-, naphthyl-(C₁-C₆ alkoxy)-,
heterocyclic-(C₁-C₆ alkoxy)-, or unsaturated
heterocyclic-(C₁-C₆ alkoxy)-, hydroxy, halo, C₁-C₆
15 alkyl, C₁-C₆ alkoxy, trifluoromethyl, nitro, amino,
cyano, C₁-C₆ alkylamino, and C₁-C₆ alkylthio;

20 R³ is hydrogen, nitro, C₁-C₆ alkanoyl, amino, C₁-C₆ alkyl,
C₁-C₆ alkoxy, C₃-C₈ cycloalkyl, heterocyclic, unsaturated
heterocyclic, halo, C₁-C₆ alkylthio, hydroxy-(C₁-C₆ alkylidenyl)-, hydroxy-(C₁-C₆ alkylidenyl)amino-, R⁴R⁵N-,
R⁴R⁵N-(C₁-C₆ alkylidenyl)-, R⁴R⁵N-(C₁-C₆ alkoxy)-, hydroxy-(C₁-C₆ alkyl)-, heterocyclic-(C₁-C₆ alkoxy)-, amino(C₁-C₆ alkylidenyl)-, or trifluoromethyl,

25 where R⁴ and R⁵ are independently selected from the
group consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkanoyl, aryl, heterocyclic, unsaturated
heterocyclic, aryl(C₁-C₆ alkylidenyl)-, heterocyclic(C₁-C₆ alkylidenyl)-, unsaturated heterocyclic(C₁-C₆ alkylidenyl)-, and hydrogen or R⁴ and R⁵ combine to
30 form C₃-C₈ cycloalkyl,

any one of which alkyl or alkoxy groups may be substituted with one or more halo, amino, or nitro, and

5 any one of which aryl, unsaturated heterocyclic, or heterocyclic groups may be substituted with one, two, or three moieties independently selected from group consisting of hydroxy, halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, trifluoromethyl, nitro, amino, cyano, C₃-C₈ cycloalkyl, C₁-C₆ alkylamino, and C₁-C₆ alkylthio;

10

15 with the proviso that not more than one of R¹ and R² may be hydrogen;

or a pharmaceutically acceptable salt or solvate thereof.

2. A method as claimed in Claim 1 employing

20 employing 1-benzyl-2-(3,4,5-trimethoxyphenyl)-6-[2-(4-morpholinyl)ethoxy]benzimidazole, 1-benzyl-2-(3,4,5-trimethoxyphenyl)-6-[2-(1-piperidinyl)ethoxy]benzimidazole, 1-benzyl-2-(3,4,5-trimethoxyphenyl)-6-[2-(1-pyrrolidinyl)ethoxy]benzimidazole, 1-benzyl-2-(3,4,5-trimethoxyphenyl)-6-[2-(1-hexamethyleneiminyl)ethoxy]benzimidazole, 1-benzyl-2-(3,4,5-trimethoxyphenyl)-6-[3-(1-piperidinyl)propoxy]benzimidazole, 1-benzyl-2-(3,4,5-trimethoxyphenyl)-6-[2-[4-(piperidin-1-yl)piperdin-1-yl]ethoxy]benzimidazole, 1-benzyl-2-(3,4,5-trimethoxyphenyl)-6-[2-(4-methyl-1-piperazinyl)ethoxy]benzimidazole, 1-benzyl-2-(3-methylphenyl)-6-[2-(1-pyrrolidinyl)ethoxy]benzimidazole, 1-benzyl-2-(3-methylphenyl)-6-[3-(piperidin-1-yl)propoxy]benzimidazole, 1-benzyl-2-(3-methylphenyl)-6-[3-(morpholin-4-yl)propoxy]benzimidazole, 1-benzyl-2-(3-methylphenyl)-6-[3-(pyrrolidin-1-yl)propoxy]benzimidazole, 1-benzyl-2-(3-methylphenyl)-6-[3-(hexamethyleneimin-1-yl)propoxy]benzimidazole, 1-benzyl-2-(3-

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methylphenyl)-6-[3-(heptamethyleneimin-1-yl)propoxy]benzimidazole, 1-benzyl-2-(3-methylphenyl)-6-[2-(4-methyl-piperazin-1-yl)ethoxy]benzimidazole, 1-(2-trifluoromethylbenzyl)-2-(3,4,5-trimethoxyphenyl)-6-[2-(piperidin-1-yl)ethoxy]benzimidazole, 1-(2-trifluoromethylbenzyl)-2-(3,4,5-trimethoxyphenyl)-6-[3-(piperidin-1-yl)propoxy]benzimidazole, 1-(2-trifluoromethylbenzyl)-2-(3,4,5-trimethoxyphenyl)-6-[2-(pyrrolidin-1-yl)ethoxy]benzimidazole, 1-(2-trifluoromethylbenzyl)-2-(3,4,5-trimethoxyphenyl)-6-[2-(morpholin-4-yl)ethoxy]benzimidazole, 1-(2-bromobenzyl)-2-(3,4,5-trimethoxyphenyl)-6-[2-(piperidin-1-yl)ethoxy]benzimidazole, 1-(2-trifluoromethylbenzyl)-2-(3-methylphenyl)-6-[2-(piperidinyl-1-yl)ethoxy]benzimidazole, 1-(2-bromobenzyl)-2-(3-methylphenyl)-6-[2-(piperidinyl-1-yl)ethoxy]benzimidazole, 1-(2-trifluoromethylbenzyl)-2-(3,4-dimethylphenyl)-6-[2-(piperidin-1-yl)ethoxy]benzimidazole, 1-(2-bromobenzyl)-2-(3,4-dimethylphenyl)-6-[2-(piperidin-1-yl)ethoxy]benzimidazole, or 1-(2-bromobenzyl)-2-(3,5-dimethylphenyl)-6-[2-(piperidin-1-yl)ethoxy]benzimidazole, or a pharmaceutically acceptable salt or solvate thereof.

20

3. A method as claimed in **Claim 1** employing employing 1-benzyl-2-(3,4,5-trimethoxyphenyl)-6-[1-methyl-2-(N,N-dimethylamino)ethoxy]benzimidazole, 1-benzyl-2-(3,4,5-trimethoxyphenyl)-6-[2-(N,N-dimethylamino)ethoxy]benzimidazole, 1-benzyl-2-(3,4,5-trimethoxyphenyl)-6-[3-(N,N-dimethylamino)propoxy]benzimidazole, 1-benzyl-2-(3,4,5-trimethoxyphenyl)-6-[2-(N,N-diisopropylamino)ethoxy]benzimidazole, 1-benzyl-2-(3-methylphenyl)-6-[2-(N,N-dimethylamino)ethoxy]benzimidazole, 1-benzyl-2-(3-methylphenyl)-6-[2-(N,N-diethylamino)ethoxy]benzimidazole, 1-benzyl-2-(3-methylphenyl)-6-[3-(N,N-dimethylamino)propoxy]benzimidazole, 1-benzyl-2-(3-methylphenyl)-6-[2-(N,N-isopropylamino)ethoxy]benzimidazole, 1-

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benzyl-2-(3-methylphenyl)-6-[2-(N,N-dibenzylamino)ethoxy]benzimidazole, 1-benzyl-2-(3-methylphenyl)-6-[3-(N,N-dimethylamino)propoxy]benzimidazole, 1-benzyl-2-(3-methylphenyl)-6-[2-(N,N-dimethylamino)propoxy]-benzimidazole, 1-(2-trifluoromethylbenzyl)-2-(3,4,5-trimethoxyphenyl)-6-[2-(N,N-dimethylamino)propoxy]-benzimidazole, 1-(2-trifluoromethylbenzyl)-2-(3,4,5-trimethoxyphenyl)-6-[2-(N,N-dimethylamino)ethoxy]-benzimidazole, 1-(2-trifluoromethylbenzyl)-2-(3,4,5-trimethoxyphenyl)-6-[3-(N,N-dimethylamino)propoxy]-benzimidazole, 1-(2-trifluoromethylbenzyl)-2-(3,4,5-trimethoxyphenyl)-6-[2-(N,N-diisopropylamino)ethoxy]-benzimidazole, 1-(2-bromobenzyl)-2-(3,4,5-trimethoxyphenyl)-6-[2-(N,N-dimethylamino)propoxy]benzimidazole, 1-(2-bromobenzyl)-2-(3,4,5-trimethoxyphenyl)-6-[2-(N,N-dimethylamino)ethoxy]benzimidazole, 1-(2-bromobenzyl)-2-(3,4,5-trimethoxyphenyl)-6-[3-(N,N-dimethylamino)propoxy]benzimidazole, 1-(2-bromobenzyl)-2-(3,4,5-trimethoxyphenyl)-6-[2-(N,N-diisopropylamino)ethoxy]benzimidazole, 1-(2-trifluoromethylbenzyl)-2-(3-methylphenyl)-6-[3-(N,N-dimethylamino)propoxy]benzimidazole, 1-(2-bromobenzyl)-2-(3-methylphenyl)-6-[2-(N,N-dimethylamino)ethoxy]benzimidazole, 1-(2-bromobenzyl)-2-(3-methylphenyl)-6-[3-(N,N-dimethylamino)propoxy]benzimidazole, 1-(2-bromobenzyl)-2-(3-methylphenyl)-6-[2-(N,N-dimethylamino)ethoxy]benzimidazole, 1-(2-trifluoromethylbenzyl)-2-(3,4-dimethylphenyl)-6-[2-(N,N-diisopropylamino)ethoxy]benzimidazole, 1-(2-bromobenzyl)-2-(3,4-dimethylphenyl)-6-[2-(N,N-dimethylamino)ethoxy]benzimidazole, 1-(2-bromobenzyl)-2-(3,4-dimethylphenyl)-6-[2-(N,N-diisopropylamino)ethoxy]benzimidazole, 1-(2-bromobenzyl)-2-(3,4-dimethylphenyl)-6-[2-(N,N-dimethylamino)ethoxy]benzimidazole, 1-(2-bromobenzyl)-2-(3,5-dimethylphenyl)-6-[2-(N,N-dimethylamino)ethoxy]benzimidazole, 1-(2-

bromobenzyl)-2-(3,5-dimethylphenyl)-6-[1-methyl-2-(N,N-dimethylamino)ethoxy]benzimidazole, 1-(2-bromobenzyl)-2-(3,5-dimethylphenyl)-6-[2-(N,N-diisopropylamino)ethoxy]benzimidazole, or 1-(2-bromobenzyl)-2-(3,5-dimethylphenyl)-6-[3-(N,N-dimethylamino)propoxy]benzimidazole, or a pharmaceutically acceptable salt or solvate thereof.

4. A compound as described in any one of **Claims 1 to 3**, for use in treating or preventing sleep apnea.

10

5. A pharmaceutical formulation containing, as an active ingredient, a compound as described in any one of **Claims 1 to 3**, adapted for use in the treatment or prevention of sleep apnea.

15

6. The use of a compound as described in any one of **Claims 1 to 3**, for the manufacture of a medicament for the treatment or prevention of sleep apnea.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/03113

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/415
US CL :514/394

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/394

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,356,934 A (ROBERTSON et al) 18 October 1994 (18/10/94), see entire document, especially claim 1.	1-6 (in part)

 Further documents are listed in the continuation of Box C. See patent family annex.

• Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other event		
P document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

11 JUNE 1997

Date of mailing of the international search report

10 JUL 1997

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INTERNATIONAL SEARCH REPORT

International application No. PCT/US97/03113

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: 1-6 (parts)
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Please See Extra Sheet.

3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/03113

BOX I. OBSERVATIONS WHERE CLAIMS WERE FOUND UNSEARCHABLE
2. Where no meaningful search could be carried out, specifically:

The multitude of variables and their permutations and combinations (e.g. R1, R2, the proviso, etc.) result in claimed subject matter that is so broad in scope that it is rendered virtually incomprehensible and thus no meaningful search can be given. Note also that the claimed subject matter lacks a significant structural element qualifying as the special technical feature that clearly defines a contribution over the art. The subject matter claimed contains a benzimidazole group which does not define a contribution over the prior art. Therefore, the first discernible invention, which is the method of treating sleep apnea using the compound of Example 1, has been searched.